

# **Cognitive decline during acute hypoglycaemia**

Vincent McAulay

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**TO KAREN**



(a) This thesis was composed by Dr Vincent McAulay.

(b) Studies 1 to 4 were performed, written and analysed by myself. In Study 1, Dr Stewart Ferguson, and the staff of the Wellcome Trust Clinical Research Facility, Edinburgh, assisted me with the glucose clamp procedure and the administration of cognitive function tests. In Studies 2 and 3, Dr Andrew Sommerfield helped with the clamping and cognitive tests. Dr Stewart Ferguson wrote the study protocol and gained ethical approval for study 4.

(c) I hold the degree of MBChB.

(d) This thesis has not been submitted for any other degree, diploma or professional qualification.

**V McAulay**

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# THE UNIVERSITY OF EDINBURGH

## ABSTRACT OF THESIS

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Name of  
Candidate:

VINCENT MC AULAY

Address :

Postal  
Code:

G1 10L

Degree:

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Hypoglycaemia is a common side effect of treatment with insulin in people with type 1 diabetes. Because of its detrimental effects on the brain, acute hypoglycaemia is a major limiting factor in achieving strict glycaemic control. Therefore, there is a need to study the effects of hypoglycaemia on brain function so that clinical practice may be better informed, and to look for novel methods of reducing hypoglycaemia. The initial chapters of this thesis describe the clinical and physiological aspects of hypoglycaemia, followed by a review of the literature on the effects of acute hypoglycaemia on cognitive function. The subsequent chapters describe original research studies in subjects with and without diabetes, which examine the effects of acute hypoglycaemia on aspects of cognitive function and the prevention of hypoglycaemia.

In Studies 1 to 3, a hyperinsulinaemic glucose clamp was used to either maintain euglycaemia (blood glucose 4.5 mmol/l) or induce hypoglycaemia (2.6 mmol/l) in both healthy adults (n=20), and subjects with type 1 diabetes (n=16). A cognitive test battery was administered to examine aspects of attention, intelligence, motivation, affect and subjective cognition. Hypoglycaemia induced a significant deterioration in tests sensitive to both visual and auditory selective attention, and attentional flexibility deteriorated (Studies 1 and 2). Intelligence scores did not deteriorate during hypoglycaemia (Studies 1 and 2). In Study 3, hypoglycaemia increased task-irrelevant interference and self-focus of attention, but motivation declined to a similar extent during both study conditions. Hypoglycaemia produced a negative mood state with a significant fall in energy levels and a concomitant rise in anxiety (Study 3). Study 4 was an open-label, comparative study of the post-prandial glucodynamics of insulin lispro, when administered either 5 minutes before or 20 minutes after a high fat/high solid phase meal, in twelve subjects with type 1 diabetes. Administration of insulin lispro after the meal reduced the risk of early postprandial hypoglycaemia, without compromising postprandial glycaemic control.

Therefore, the work in this thesis has demonstrated a differential deterioration of attentional function in humans during hypoglycaemia with no effect on non-verbal reasoning skills. Furthermore, it would appear that the brain is not only less cognitively competent and more dysphoric during hypoglycaemia, it is also more self-aware and distracted when required to perform effortful processing.

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## **SUMMARIES OF STUDIES**

## **SUMMARY OF STUDY 1**

### **Objective**

Experimentally-induced hypoglycaemia in humans causes progressive, but reversible cognitive dysfunction, but it is not known to what extent neuropsychological tests index abilities of cognitive functioning that are important in everyday life. This study sought to examine the effects of acute insulin-induced hypoglycaemia on attention and intelligence in non-diabetic humans.

### **Research Design and Methods**

A hyperinsulinaemic glucose clamp was used to achieve controlled euglycaemia (4.50 (0.22) mmol/l) and hypoglycaemia (blood glucose 2.59 (0.19) mmol/l) in 20 healthy volunteers. Subjects were studied on two occasions in a counterbalanced order. During each study condition, subjects completed parallel tests of cognitive function. Cognitive function was assessed by the Test of Everyday Attention and the Raven's Progressive Matrices.

### **Results**

Hypoglycaemia induced a significant deterioration in tests sensitive to both visual ( $p<0.01$ ) and auditory selective attention ( $p<0.01$ ). During hypoglycaemia attentional flexibility deteriorated and speed of information processing was delayed ( $p<0.0001$ ). Sustained attention was preserved and intelligence scores did not deteriorate during hypoglycaemia ( $p=0.1$ ).

## **Conclusions**

During experimental hypoglycaemia in non-diabetic humans, a significant deterioration occurs in attentional abilities, while fluid intelligence is preserved. Furthermore, there is a differential sensitivity in attentional dysfunction during hypoglycaemia, with some attentional abilities showing a marked deterioration, whereas others are unaffected. On the basis of these results it can be surmised that many complex attention tasks relevant to everyday life will be impaired during moderate hypoglycaemia.

## **SUMMARY OF STUDY 2**

### **Objective**

Acute hypoglycaemia leads to a rapid decline in mental abilities. A previous study demonstrated impairment of attentional functioning in subjects without diabetes. Therefore, the present study sought to determine whether acute insulin-induced hypoglycaemia would cause a similar pattern and degree of attentional dysfunction in people with type 1 diabetes. A further aim of the present study was to assess if acute hypoglycaemia would have no effect on non-verbal reasoning or whether a diagnosis of diabetes would act as a moderator of this important cognitive modality.

### **Research Design and Methods**

A hyperinsulinaemic glucose clamp was used to maintain euglycaemia (4.5 mmol/l) or induce hypoglycaemia (2.6 mmol/l) on separate occasions in sixteen adults with type 1 diabetes each of whom were studied on two occasions in a counterbalanced order. During each study condition, the subjects completed parallel tests of cognitive function assessed by the Test of Everyday Attention and the Raven's Progressive Matrices.

### **Results**

Significant increments were noted in the autonomic ( $p=0.002$ ), neuroglycopenic ( $p=0.001$ ), and general malaise symptom scores ( $p=0.01$ ) during hypoglycaemia. Sustained attention did not deteriorate during hypoglycaemia using either the lottery ticket test ( $p=0.26$ ) or the elevator counting test ( $p=0.15$ ), and intelligence scores, measured using the RPM, were preserved during hypoglycaemia ( $p=0.24$ ,  $\eta^2=0.12$ ). Hypoglycaemia caused a significant deterioration in tests sensitive to visual (the mean number of map symbols circled was lower during hypoglycaemia at both one minute ( $p=0.032$ ,  $\eta^2=0.29$ ) and at two minutes ( $p=0.042$ ,  $\eta^2=0.26$ ), and auditory selective attention ( $p=0.001$ ,  $\eta^2=0.59$ ). During hypoglycaemia, attentional flexibility deteriorated ( $p<0.0001$ ,  $\eta^2=0.78$ ).

## **Conclusions**

The present study has demonstrated that acute controlled hypoglycaemia causes attentional dysfunction in adults with type 1 diabetes, while there was a non-significant decline in non-verbal reasoning. The severity of the attentional deficit during acute moderate hypoglycaemia was dependent upon which attentional system was being examined. It is likely therefore that many complex cognitive tasks which involve attention will be impaired during moderate hypoglycaemia during everyday life.

## **SUMMARY OF STUDY 3**

### **Objective**

Although many aspects of cognitive function have been examined during acute hypoglycaemia, other important areas have been neglected. In particular, little information is available concerning the subjective feelings that are generated by acute hypoglycaemia. Furthermore, the conative (motivation) aspect of mind has not been explored during hypoglycaemia. Therefore, the present study examined mood, motivation and cognition in adults with type 1 diabetes using a validated measure, the Dundee Stress State Questionnaire (DSSQ).

### **Research Design and Methods**

A hyperinsulinaemic glucose clamp was used to either maintain euglycaemia (arterialised blood glucose 4.5 mmol/l) or induce hypoglycaemia (2.6 mmol/l) in sixteen adults with type 1 diabetes, each of whom were studied on two separate occasions in a counterbalanced order. During each study condition, the subjects completed parallel tests of cognitive function. The Dundee Stress State Questionnaire (DSSQ) was administered before, and after, the cognitive function tests.

### **Results**

Motivation declined to a similar extent during the euglycaemia and hypoglycaemia conditions ( $p=0.07$ ). Hypoglycaemia increased task-irrelevant ( $p=0.02$ ) interference. Self-focus of attention was much higher after hypoglycaemia than euglycaemia ( $p=0.02$ ). Hypoglycaemia produced a negative mood state with a significant fall in energy levels ( $p=0.03$ ) and a concomitant rise in anxiety level ( $p=0.05$ ). The subjective perception of concentration was unaffected during hypoglycaemia ( $p=0.14$ ), and the scores for control and confidence did not fall ( $p=0.19$ ).

## **Conclusions**

In people with type 1 diabetes, hypoglycaemia causes a state of heightened self-awareness and distraction during active mental activity. This is likely to leave fewer processing resources available to allow completion of cognitive tasks. Acute hypoglycaemia induces a state of significant worry and anxiety which is likely to have an impact on the social, personal and work activities of people with diabetes.



## **SUMMARY OF STUDY 4**

### **Objective**

Fast-acting insulin analogues have a more rapid onset and shorter duration of action than human soluble insulin. Although these insulins are usually injected immediately before meals, a delayed rise in postprandial blood glucose or a reduced glycaemic response to a meal may increase the risk of early postprandial hypoglycaemia. The aim of the present study was to examine the effect of either pre- or post-prandial administration of insulin lispro on the pharmacodynamics of blood glucose following the consumption of a high fat, solid-phase meal, to determine which time of administration of insulin was less likely to promote early post-prandial hypoglycaemia.

### **Research Design and Methods**

12 subjects with type 1 diabetes were studied on two separate occasions. All subjects ingested a high fat, solid-phase meal as a standardised (weighed) portion of fried fish and chipped potatoes. Insulin lispro was administered 5 minutes before the meal on one occasion and 20 minutes postprandially on another. The magnitude and temporal pattern of the postprandial glucose excursions were measured.

### **Results**

The glycaemic excursion over time was greater when insulin lispro was administered after the test meal but failed to achieve statistical significance ( $p=0.059$ ). Pre-prandial lispro produced a cumulative decline in post-prandial blood glucose (maximal decrement of blood glucose below baseline (mean (SD)  $-1.7$  ( $2.4$ ) mmol/l), whereas blood glucose increased after the meal when lispro was administered post-prandially (maximal increment of blood glucose above baseline  $+2.2$  ( $1.3$ ) mmol/l). When lispro was administered before the meal, post-prandial hypoglycaemia developed in three subjects. Hypoglycaemia did not occur when lispro was administered post-prandially.



## **Conclusions**

Administration of insulin lispro 20 minutes after a high fat, solid-phase meal did not provoke a postprandial fall in blood glucose, and did not result in pronounced postprandial hyperglycaemia. In conclusion, when a meal contains a high content of fat in solid-phase, administration of insulin lispro after the meal may reduce the risk of early postprandial hypoglycaemia, without compromising postprandial glycaemic control.

**PART I**  
**BACKGROUND**

**CHAPTER 1**  
**PATHOPHYSIOLOGICAL AND CLINICAL ASPECTS OF**  
**HYPOGLYCAEMIA**

## 1.1 BACKGROUND

The successful isolation of insulin by Frederick Banting and John Macleod, with the collaboration of Charles Best and James Collip, in Toronto, was in the early 1920s. Thereafter, when insulin was introduced to treat human diabetes, the symptoms of hypoglycaemia soon became apparent. A 'characteristic train of symptoms' and signs were noted as the blood glucose was lowered below normal, and this response was described as a 'hypoglycaemic reaction' [Fletcher & Campbell, 1922, Banting et al, 1923]. As the blood glucose declined further cognitive dysfunction became prominent, with a rapid deterioration in mental functions, unless appropriate corrective action was taken [Fletcher & Campbell, 1922].

Since the discovery of insulin more than 80 years ago considerable advances in insulin therapy have occurred: most recently analogues of human insulin have been produced by manipulation of the amino acid sequence of the insulin molecule; these have included rapid- and short-acting analogues (lispro and aspart), and long-acting insulins (insulin glargine and insulin detemir) [McAulay & Frier, 2003]. Despite these major advances that have occurred in the treatments for diabetes, people who have type 1 diabetes still fail to achieve recommended glycaemic targets. However, if the risk (and fear) of hypoglycaemia was not always present, people with diabetes could achieve normal blood glucose levels. Instead, they are often exposed to suboptimal glucose concentrations, and are thus precluded from the full attainment of the well-established benefits of strict glycaemic control [The DCCT, 1993]. A fundamental problem with current treatment regimens is that they do not provide insulin replacement that is blood glucose-regulated; whereas the glucose lowering action of endogenous insulin occurs in minutes, even the shortest acting insulin analogues used to treat diabetes, have a duration of action that is measured in hours. Therefore, hypoglycaemia causes recurrent symptomatic and often disruptive episodes in most people with type 1 diabetes, and remains

the limiting factor in achieving normal glucose levels in the treatment of diabetes [Cryer, 1993a].

## **1.2 DEFINITION OF HYPOGLYCAEMIA**

It is not possible to study hypoglycaemia without actually determining what 'hypoglycaemia' means for the individual with diabetes. Hypoglycaemia can be defined as an arbitrary biochemical level, e.g. blood glucose of 3.5 mmol/l or below, or on the basis of symptoms of hypoglycaemia. The latter can be classed into degrees of severity depending on the physical effects and the need for help from another person to restore a normal glucose. Hence, hypoglycaemia can be mild, and self-treated by the patient (mild symptomatic hypoglycaemia), or severe, requiring the help of others for recovery (severe hypoglycaemia). The latter does not necessitate whether the patient is conscious, in a coma or convulsing, nor the mode of treatment, whether it be food, intravenous glucose or glucagon. Hypoglycaemia can also be asymptomatic and detected on biochemical testing (biochemical hypoglycaemia). The latter poses particular problems because it can only be identified by measuring the blood glucose so will often go undetected, especially during sleep (usually nocturnal hypoglycaemia).

These definitions of hypoglycaemia, especially the numerical biochemical level, may appear to be straightforward, but they present numerous problems in both clinical and research practice. For example, in many people with insulin-treated diabetes the perception of symptoms becomes altered or diminished, either with increasing duration of diabetes, or relating to periods of recent metabolic change, and they develop the syndrome of impaired awareness of hypoglycaemia [Frier & Fischer, 1999]. By contrast, people with poor glycaemic control and an elevated HbA1c may experience symptoms of hypoglycaemia when blood glucose declines within the hyperglycaemic range [Maddock & Krall, 1953, Boyle et al, 1988, Jones et al, 1991, Kinsley et al, 1995].

In clinical practice, the most important definition of hypoglycaemia is that which the patient understands. Some patients assume that they have not suffered hypoglycaemia unless they have been in coma. Therefore, it is important to be clear what is meant by hypoglycaemia when discussing this with people with diabetes. Diabetes UK has recommended that individuals with diabetes should maintain a blood glucose above 4.0 mmol/l wherever possible [www.diabetes.org.uk]. In the clinic, a useful question may be, "How often do you experience symptoms of a low blood glucose during an average week?" Some patients consider that only severe hypoglycaemia, i.e. the need for external assistance, or even loss of consciousness, to represent a 'hypo'. To clarify the frequency of these episodes the patient could be asked, "How many times in the last year have you had a low blood glucose when you have required help for treatment?" If an individual is experiencing frequent symptomatic hypoglycaemia, it is important to seek biochemical verification in view of the non-specific nature of symptoms.

### **1.3 FREQUENCY OF HYPOGLYCAEMIA**

#### **1.3.1 Frequency of mild hypoglycaemia**

People with type 1 diabetes suffer an average of two episodes of symptomatic hypoglycaemia per week, amounting to thousands of such episodes over a lifetime of diabetes treatment [Pramming et al, 1991]. However, many episodes of mild hypoglycaemia that occur in the community go unrecognised so that this figure is likely to be a significant underestimate. This may well be a particular problem during the night, and it is unsurprising that the frequency of nocturnal hypoglycaemia is high. In one of the first overnight studies, Gale & Tattersall [1979] found at least one blood glucose value below 2.0 mmol/l in half of 39 patients with diabetes treated with insulin, and in three-quarters of these episodes the hypoglycaemia lasted for three or more hours. These results were confirmed by subsequent investigators, where nocturnal hypoglycaemia occurred in 10-56% of overnight profiles [Dornan et al, 1981, Pramming et al,



1985, Whincup & Milner, 1987, Bendtson et al, 1988, Shalwitz et al, 1990, Vervoort et al, 1996]. Rather worryingly, this nocturnal hypoglycaemia was asymptomatic in 25-70% of episodes and lasted for up to 6 hours in some.

Few large-scale studies have recorded the frequency of hypoglycaemic episodes in people with type 2 diabetes treated with insulin over a protracted period of treatment. The proportion of patients experiencing hypoglycaemia during the first 10 years of the UKPDS [1998] is shown in table 1.1.

**Table 1.1** Proportion of patients with type 2 diabetes experiencing hypoglycaemia per year in UK Prospective Diabetes Study over 10 years of the study by principal treatment regimen (mean figures are shown) (derived from UKPDS, 1998). Reproduced from *Diabetes in Old Age* 2<sup>nd</sup> edition, 2001 (eds AJ Sinclair and P Finucane). Copyright 2001, John Wiley & Sons Limited, reproduced with permission

	One or more major <sup>a</sup> episodes of hypoglycaemia (%)	Any episode of hypoglycaemia (%)
Diet	0.1	1.2
Chlorpropamide	0.4	11.0
Glibenclamide	0.6	17.7
Insulin	2.3	36.5

<sup>a</sup>major hypoglycaemia required third-party help or medical intervention

### **1.3.2 Frequency of severe hypoglycaemia**

Edwin Gale proposed the 'Rule of Thirds' to hypoglycaemic coma; this states that one in three patients will have a hypoglycaemic coma at some point in their life, that one in three of these (10% of the total) will have had a coma in the previous year, and that one in three of these (i.e. 2-3% of the total) have a significant disruption of their lives from recurrent hypoglycaemia coma [Gale, 1986]. However, severe hypoglycaemia can occur without coma and, therefore, around one third of people with type 1 diabetes will experience an episode of severe hypoglycaemia per annum [The Diabetes and Complications Trial Research Group, 1993, Reichard et al, 1991, MacLeod et al, 1993]. Representative event rates for severe hypoglycaemia during aggressive insulin therapy in type 1 diabetes range from 62 [The DCCT, 1991] to 170 [MacLeod et al, 1993] episodes per 100 patient-years. This contrasts with aggressive insulin therapy for type 2 diabetes, which range from 3 [Abaira et al, 1995] to 73 [MacLeod et al, 1993] episodes per 100 patient-years, although a recent, short prospective survey in Dundee demonstrated a rate of severe hypoglycaemia of 0.35 events per patient per year [Donnelly et al, 2005]. In that study, a history of previous hypoglycaemia and long duration of diabetes was highly predictive of further events [Donnelly et al, 2005]. However, in a local series, the frequencies of severe hypoglycaemia were similar in type 1 and type 2 diabetes matched for duration of insulin therapy [Hepburn et al, 1993a]. Therefore, given the progressive insulin deficiency that occurs in type 2 diabetes [UKPDS, 1998], iatrogenic hypoglycaemia becomes a more frequent clinical problem for people with type 2 diabetes as they approach the insulin-deficient end of the spectrum.



## **1.4 PHYSIOLOGICAL RESPONSES TO HYPOGLYCAEMIA**

### **1.4.1 Effects of glucose deprivation on CNS metabolism**

Glucose is an obligate metabolic fuel for the brain under normal physiological conditions. Because the brain cannot synthesise glucose or store more than a few minutes supply as glycogen, it is critically dependent on a continuous supply of glucose from the blood. Although the brain constitutes only 2% of body weight, it consumes 20% of the body's oxygen and receives 15% of its cardiac output [Sokaloff, 1989]. Under normal circumstances with intact glucose homeostasis, counterregulatory responses are usually very effective so that hypoglycaemia rarely occurs in healthy individuals, even after prolonged fasting. Therefore, blood glucose concentrations are maintained within a narrow range despite wide variability in carbohydrate intake and physical activity. To maintain this balance, acute hypoglycaemia induces a series of hormonal, neurophysiological, symptomatic and cognitive changes that occur at different and defined blood glucose concentrations.

### **1.4.2 Counterregulation**

In humans, several mechanisms have evolved to maintain glucose homeostasis and so protect the integrity and function of the brain [Cryer, 1993a]. Falling arterial glucose concentrations activates a characteristic hierarchy of responses, commencing with the suppression of endogenous insulin secretion, the release of several counterregulatory hormones, and the subsequent development of characteristic symptoms (figure 1.1). These alert the individual to the development of hypoglycaemia, so allowing them to take early and appropriate action to assist recovery. Such protective responses are usually very effective in maintaining the arterial blood glucose concentration within the normal range, which protects the brain from exposure to neuroglycopenia caused by protracted glucose deprivation. Glucose counterregulation is controlled from centres within the brain (mainly the ventromedial hypothalamus) assisted by activation of central autonomic nervous centres within the hypothalamus with subsequent stimulation of the peripheral sympatho-adrenal system. This contributes to

glucose counterregulation through the peripheral actions of catecholamines and also by the generation of characteristic autonomic warning symptoms [Cryer 1993a].

Although glucagon (secreted by pancreatic alpha cells independently of control by the brain) is the most potent counterregulatory hormone, the role of adrenaline release from the adrenal medullae, becomes paramount if the secretory response of glucagon is deficient [Gerich, 1988]. Other counterregulatory hormones, released through activation of the hypothalamic-



**Figure 1.1** Acute hypoglycaemia induces a series of hormonal, neurophysiological, symptomatic and cognitive changes that occur at different and defined blood glucose concentrations. Reproduced from Textbook of Diabetes 2<sup>nd</sup> edition 1997 (eds J Pickup & G Williams) with permission of Blackwell Science Ltd. Copyright 1997 Blackwell Science Ltd

pituitary axis, such as cortisol and growth hormone have greater importance in promoting recovery from prolonged hypoglycaemia [Cryer 1993b]. Glucagon stimulates hepatic glycogenolysis, releasing glucose from glycogen stored in the liver, and also promotes gluconeogenesis from three-carbon precursors such as alanine, lactate and glycerol [Frizell et al, 1988]. The energy for this process is provided by the hepatic oxidation of free fatty acids that are released by lipolysis. Catecholamines inhibit insulin secretion, diminish the peripheral uptake of glucose, stimulate lipolysis and proteolysis and promote glycogenolysis in peripheral muscle to provide lactate, which is utilised for gluconeogenesis in the liver and kidney [Frizell et al, 1988].

#### **1.4.3 Symptoms of hypoglycaemia**

Most symptoms experienced during hypoglycaemia are generated either by the direct effects of a low blood glucose on the brain (neuroglycopenia) or through activation of the autonomic nervous system. Common autonomic symptoms are sweating, tremor, pounding heart, anxiety and hunger, whereas neuroglycopenic symptoms include drowsiness, poor concentration, confusion, difficulty speaking and incoordination [Deary, 1999]. Non-specific symptoms are nausea and headache [Deary, 1999]. The symptoms of hypoglycaemia are discussed in more detail in section 1.5.

#### **1.4.4 Glycaemic thresholds**

Different physiological responses occur when the declining blood glucose reaches specific concentrations. Although these glycaemic thresholds are readily reproducible in non-diabetic humans [Vea et al, 1992], they are dynamic and can be modified in people with diabetes. In non-diabetic humans the glycaemic threshold at which the secretion of most counterregulatory hormones is triggered is an arterialised blood glucose of approximately 3.8 mmol/l, so that counterregulation is usually activated when blood glucose falls below the normal range. Counterregulation therefore occurs at a higher blood glucose than

that at which the symptomatic response to hypoglycaemia occurs (3.0 mmol/l) and before the onset of cognitive dysfunction (2.8 mmol/l) (figure 1.1). It is important to be clear on the semantics used to describe these alterations in glycaemic threshold. When the blood glucose required to initiate a given response is lower than usual, the glycaemic threshold is said to be raised or elevated. Therefore, a more profound hypoglycaemic stimulus is required to trigger a response.

## **1.5 SYMPTOMS OF HYPOGLYCAEMIA**

When the brain is deprived of glucose various symptoms are generated. Awareness of the symptoms of hypoglycaemia provides the patient with diabetes with an early warning of a progressive decline in blood glucose, therefore perception of their onset usually allows appropriate action to be taken before the effects of neuroglycopenia become disabling.

### **1.5.1 Classification of symptoms**

Symptoms have been categorised using two principal approaches: (1) physiological studies in which symptoms are recorded and measured during experimentally-induced hypoglycaemia, often using pharmacological blockade and (2) multivariate statistical analyses of symptoms described in field studies or during experimentally-induced hypoglycaemia.

#### **Physiological methods**

*Autonomic symptoms:* In addition to observations in people with diabetes, studies have been performed in non-diabetic subjects and in people with various forms of autonomic denervation. People who have suffered cervical cord transection develop tetraplegia and a pre-ganglionic sympathectomy. They experience neuroglycopenic symptoms during acute hypoglycaemia but autonomic warning symptoms are absent [Corrall et al, 1979, Mathias et al, 1979, Frier, 1981]. However, patients who have undergone bilateral adrenalectomy [Ginsburg & Paton, 1956, Altorfer et al, 1981] or splanchnicectomy [French & Kilpatrick,



1955] do not secrete adrenaline in response to hypoglycaemia, and retain autonomic symptoms. Their autonomic neural pathways are otherwise intact, allowing normal stimulation of end-organs, thus demonstrating that the secretion of adrenaline is not vital to generate most autonomic symptoms. The autonomic origin of the symptoms of 'feeling shaky/tremulous', 'pounding heart' and 'feeling nervous/anxious' was also confirmed during glucose clamp studies using non-selective adrenoceptor blockade [Kerr et al, 1990a, Towler et al, 1993].

By contrast, the sweating response to hypoglycaemia [French & Kilpatrick, 1955, Ginsburg & Paton, 1956, Altorfer et al, 1981, Frier, 1981, Corrall et al, 1983, Towler et al, 1993] is mediated via cholinergic sympathetic fibres. The perception of hunger is generated through an incompletely understood behavioural mechanism involving hypothalamic control and the autonomic nervous system [Leibowitz, 1975, Frances et al, 1983, Bray, 1984, Krauchi et al, 1984] and, during experimental hypoglycaemia, the symptom of hunger was mediated largely by cholinergic neural mechanisms [Towler et al, 1993].

*Neuroglycopenic symptoms:* Neuroglycopenia causes a rapid impairment of brain function through direct effects on neurones, and induces various symptoms. Symptoms of difficulty thinking, warmth, weakness, confusion, tiredness and drowsiness occur during hypoglycaemia, are not reduced by pan-autonomic or adrenoceptor blockade and have been classified as neuroglycopenic in type [Hepburn et al, 1993b, Towler et al, 1993]. The symptoms of faintness, dizziness, difficulty speaking and blurring of vision were not affected by pharmacological blockade [Towler et al, 1993] and are also considered to be neuroglycopenic.

### **Statistical approaches: Factor analysis**

The set of statistical procedures known as factor analysis has been utilised to classify the symptoms produced during acute experimental hypoglycaemia into autonomic or neuroglycopenic groups [Berlin et al, 1987, Egger et al, 1991]. A retrospective study of 295 ambulant subjects with insulin-treated diabetes demonstrated five discrete groups of symptoms of hypoglycaemia [Hepburn et al, 1992], whereas a further study of 598 people using confirmatory factor analysis suggested a three factor model [Deary et al, 1993a]. These three groups of symptoms were described as 'neuroglycopenic', 'autonomic' and 'general malaise'. This validated three-factor model contains 11 common symptoms (referred to as the 'Edinburgh Hypoglycaemia Scale'), and application of these statistical techniques has revealed age-specific differences in the classification and frequency of common hypoglycaemic symptoms.

### **1.5.2 Symptoms in different age groups**

The symptoms of hypoglycaemia vary depending on the age of the individual (table 1.2). This observation is of relevance both to clinical practice and to the interpretation and design of research studies.

#### *Children*

In very young children, neuroglycopenic and non-specific symptoms are more common and autonomic symptoms are reported less frequently, if at all [Tupola & Rajantie, 1998]. In a prospective study of 161 children and adolescents with type I diabetes, the most commonly reported symptoms of hypoglycaemia were weakness, tremor, hunger and drowsiness [Tupola & Rajantie, 1998]. In studies of hypoglycaemia symptoms in children using a modified hyperinsulinaemic glucose clamp, hunger, sleepiness, "feeling low", sweating and shakiness were reported with the greatest frequency [Ryan et al, 1990, Jones et al, 1991, Bjorgass et al, 1997].

**Table 1.2**      Features of hypoglycaemia in children and the elderly

<i>SYMPTOM CLASS</i>	<b>CHILDREN</b>	<b>ELDERLY</b>	<b>ADULTS</b>
<i>Autonomic</i>	hunger trembling pallor	sweating shaking pounding heart anxiety	sweating shaking palpitations hunger
<i>Neurological/ Neuroglycopenic</i>	dizziness poor concentration drowsiness weakness	weakness drowsiness poor concentration dizziness confusion lightheadedness	confusion drowsiness odd behaviour speech difficulty incoordination
<i>Behavioural</i>	tearful confused tired irritable aggressive	-----	-----
<i>Neurological</i>	-----	unsteady poor coordination double vision blurred vision slurred speech	-----
<i>Non-specific</i>	-----	-----	malaise headache

Data derived from Japp et al [1998], McCrimmon et al [1995], Ross et al [1998], Deary et al [1993a]



Using principal components analysis it was observed that weakness was the symptom most commonly reported by children (81%) [McCrimmon et al, 1995] and the sign most frequently observed by parents was pallor (88%). Both the children and their parents reported a cluster of symptoms relating to behavioural change, which included irritability, being argumentative and becoming naughty. In keeping with other studies [McCrimmon et al, 1995, Ross et al, 1998] there was close agreement between children and their parents concerning the relative frequency and intensity of each symptom reported. Similar behavioural symptoms in children have been described previously [Macfarlane et al, 1989, Macfarlane & Smith, 1988].

### *Elderly people*

In studies of experimental hypoglycaemia in elderly non-diabetic subjects, fewer individual symptoms were documented, the intensity of hypoglycaemic symptoms was diminished and subjective awareness of hypoglycaemia was reduced [Brierley et al, 1995, Matyka et al, 1997]. Elderly people with type 2 diabetes also have a more limited perception of autonomic symptoms of hypoglycaemia which have a lower intensity than those reported by non-diabetic elderly subjects [Meneilly et al, 1994]. Limited recognition of symptoms may partly be a consequence of inadequate education in elderly people with diabetes, whose relatives have also been shown to lack knowledge of the symptoms of hypoglycaemia [Mutch & Dingwall-Fordyce, 1985, Thomson et al, 1991].

Factor Analysis of the hypoglycaemia symptoms of elderly people have revealed distinct neuroglycopenic and autonomic groupings while headache and nausea, typical symptoms of the 'general malaise' factor experienced by younger adults, were rare [Japp et al, 1998]. This is of relevance in the clinical situation because neurological symptoms of hypoglycaemia in elderly people may be misinterpreted as representing transient cerebral ischaemia, vasovagal syncope or even the effects of a cardiac arrhythmia. Hypoglycaemia may not therefore be recognised and the cause of the symptoms not addressed.

Therefore, the frequency of hypoglycaemia is probably underestimated in this age group.

### **1.5.3 Variability of symptoms**

A few general statements concerning symptoms of hypoglycaemia can be made:

- The symptom profile provoked by hypoglycaemia is idiosyncratic and varies in character and intensity between individuals [Pennebaker et al, 1981, Cox et al, 1983, 1985].
- Although no single symptom is present consistently during hypoglycaemia in all people with diabetes, some symptoms are more common than others [Cox et al, 1983].
- People with insulin-treated diabetes should be familiar with their own symptom profile, thus enabling them to perceive the early onset of hypoglycaemia.

Unfortunately, no single symptom has been shown to correlate significantly with a specific blood glucose concentration in humans [Pennebaker et al, 1981]. Thus, the idiosyncratic nature of symptoms of hypoglycaemia is important when educating people with newly diagnosed diabetes or those commencing insulin treatment, ensuring that symptoms are highlighted that are of personal relevance. However, reliance on symptom reporting can be misleading as some seemingly discriminatory symptoms of hypoglycaemia can also occur during hyperglycaemia. For example, in one study of symptoms in people with insulin-treated diabetes, 'weakness' was significantly associated with hypoglycaemia in 27% of respondents, but in 7% was also a dependable symptom of hyperglycaemia [Pennebaker et al, 1981]. Indeed, all of the recorded symptoms of hypoglycaemia may occur in other circumstances and can therefore be considered as 'non-specific'. Examples of this are 'sweating' and 'pounding heart' which are normal physiological responses to exercise, but in a person with insulin-treated diabetes, may be indicative of exercise-induced hypoglycaemia. The potential for misinterpretation of the symptoms of hypoglycaemia in such

situations is significant, and the only reliable way of ascertaining the cause is to measure blood glucose.

Although the intensity of individual symptoms is fundamental to detecting the onset of hypoglycaemia, the number of warning symptoms that are experienced is also important. People who had one to three reliable symptom(s) of hypoglycaemia correctly recognised about one half of their episodes of hypoglycaemia (arbitrarily defined as a capillary blood glucose below 3.9 mmol/l), while those who had four or more reliable symptoms recognised hypoglycaemia in more than 70% of episodes [Cox et al, 1993a].

#### **1.5.4 Autonomic or neuroglycopenic symptoms to detect hypoglycaemia?**

It is a widely held view, both among health professionals [Cox et al, 1994a] and some people with diabetes, that the detection of hypoglycaemia is based principally on autonomic symptoms. Some investigators have firmly stated that awareness of hypoglycaemia is almost entirely the result of perception of autonomic, as opposed to neuroglycopenic, symptoms [Towler et al, 1993]. Even in the earliest clinical descriptions of hypoglycaemia, autonomic symptoms were associated with “mild reactions” whereas “severe reactions” were affiliated with neuroglycopenic symptoms, suggesting that autonomic symptoms are generated at an earlier stage in the development of hypoglycaemia [Maddock & Krall, 1953].

In studies of non-diabetic subjects that have used the stepped glucose clamp to induce experimental hypoglycaemia, autonomic symptoms were generated before neuroglycopenic symptoms, the mean difference in blood glucose concentrations being of the order of 0.5 mmol/l [Schwartz et al, 1987, Mitrakou et al, 1991]. This small difference between the glycaemic thresholds for the onset of autonomic and neuroglycopenic symptoms is unlikely to be detectable in a real life situation when the blood glucose of a person with diabetes may be

declining rapidly, and when people may not be focusing on symptoms. Therefore, when ambulant people with insulin-treated diabetes were asked about their routine experience of warning symptoms of hypoglycaemia they reported that autonomic and neuroglycopenic symptoms occurred with equal frequency [Hepburn et al, 1991]. This observation has also been made during experimentally-induced hypoglycaemia in insulin-treated diabetic subjects [Cox et al, 1993]. In contrast to autonomic symptoms, the generation of neuroglycopenic symptoms is not affected by counterregulatory hormonal failure or by preceding episodes of hypoglycaemia [Frier & Fisher, 1999]. Therefore, it would seem that autonomic and neuroglycopenic symptoms are of equal value in warning individuals of the onset of hypoglycaemia, provided that the symptoms typical to the individual are identified by them and interpreted correctly. However, with increasing duration of diabetes, autonomic symptoms may diminish in intensity and number, requiring greater reliance on neuroglycopenic cues, but the importance of the latter as valuable warning symptoms should not be underestimated [Frier & Fisher, 1999].

### **1.5.5 Factors affecting symptom generation and perception**

#### *Modulation of physiological responses*

In non-diabetic subjects glycaemic thresholds are reproducible and stable within individuals [Vea et al, 1992]. Neither gender [Cox et al, 1996], nor obesity [Vea et al, 1994], affects the glycaemic thresholds for symptoms. Potential factors that may affect the magnitude of the physiological responses to hypoglycaemia include the depth and duration of hypoglycaemia, the rate of decline of blood glucose, and, in a person with diabetes, the duration of diabetes, the quality of prevailing glycaemic control (HbA1c) and recent exposure to hypoglycaemia.

#### *Glycaemic control*

With strict glycaemic control the threshold for onset of symptoms is raised so that a more profound hypoglycaemic stimulus is required to trigger the symptomatic response for autonomic symptoms [Clarke et al, 1991, Kinsley et



al, 1995, Boyle et al, 1995, Lager et al, 1986, Amiel et al, 1988, Maran et al, 1995, Davis & Shamoon, 1991] and probably also for neuroglycopenic symptoms [Clarke et al, 1991, Maran et al, 1995]. This effect becomes evident when the HbA1c is within the non-diabetic range [Boyle et al, 1995, Kinsley et al, 1995]. The converse is true in people who have poor glycaemic control with an elevated HbA1c in whom symptoms typical of hypoglycaemia may be experienced when blood glucose declines within a hyperglycaemic range [Jones et al, 1991, Kinsley et al, 1995, Maddock & Krall, 1953, Mookan et al, 1994, Boyle et al, 1988]. These observations help to explain why many subjects with strict glycaemic control do not experience symptomatic hypoglycaemia until their blood glucose is very low, and conversely why subjects with poor glycaemic control may report experiencing symptoms of hypoglycaemia when their blood glucose is normal or elevated.

#### *Antecedent hypoglycaemia*

Fluctuations in blood glucose concentrations can influence the glycaemic threshold at which symptoms are initiated. Exposure to antecedent hypoglycaemia can diminish the degree of hormonal counterregulatory responses and symptoms to a subsequent episode of hypoglycaemia in non-diabetic subjects [Heller & Cryer, 1991, Davis & Shamoon, 1991, Widom and Simonson, 1992, Veneman et al, 1993, Mellman et al, 1994] and in people with type 1 diabetes [Lingenfelser et al, 1993, Dagogo-Jack et al, 1993, Ovalle et al, 1998]. Although the relevant studies differ considerably in design and methods of inducing hypoglycaemia, it appears that exposure to antecedent hypoglycaemia for at least 60 minutes is necessary before this exerts a significant influence on the magnitude of the symptomatic and neuroendocrine responses to a subsequent episode of hypoglycaemia occurring within the following 24 to 48 hours [Frier & Fisher, 1999]. Thus, the antecedent hypoglycaemia has to be prolonged, as exposure to repeated episodes of short-lived (15-30 minute episodes) hypoglycaemia did not demonstrate this effect [Peters et al, 1995, Davis et al, 2000]. This effect of antecedent hypoglycaemia

on the symptomatic response is probably a manifestation of cerebral adaptation to changes in prevailing blood glucose which operates through a shift of the glycaemic threshold (similar to the effect of strict glycaemic control).

#### *Nocturnal hypoglycaemia*

The effect of recurrent exposure to hypoglycaemia is one potential mechanism underlying the pathogenesis of impaired awareness of hypoglycaemia. The effects of asymptomatic nocturnal hypoglycaemia lasting for two or more hours may be of particular relevance, with two studies demonstrating a reduction in the magnitude of the symptomatic response to hypoglycaemia the following day [Veneman et al, 1993, Fanelli et al, 1998]. This is an important observation as nocturnal hypoglycaemia has been demonstrated in up to 50% of people treated with insulin, is asymptomatic in 25-75 % of episodes and may last up to 6 hours [Gale & Tattersall, 1979, Pramming et al, 1985, Bendtson et al, 1988]. Although most people treated with insulin are at risk of experiencing nocturnal hypoglycaemia, those taking fixed mixtures with their evening meal, and patients taking short-acting insulin in the late evening, may be at greater risk because of the relative hyperinsulinaemia that these insulin regimens produce in the early part of the night.

#### **1.5.6 Alteration of physical symptoms**

The physical symptoms of hypoglycaemia may be modified in several ways.

##### *Posture*

The intensity of autonomic symptoms are greater in the erect position compared to a supine posture in people with type 1 diabetes [Hirsch et al, 1991a] and in non-diabetic subjects [Maggs & Macdonald, 1994]. Hence, this facilitates understanding why some individuals do not recognise subtle symptoms of hypoglycaemia while they are lying in bed, but the symptoms become apparent soon after rising. In addition, this is of importance in interpreting studies of

experimentally-induced hypoglycaemia, most of which are performed with subjects in a supine position.

### *Medications*

Hypnotic medications and alcohol may impair the ability to perceive and interpret symptoms of hypoglycaemia [Kerr et al, 1990b]. By contrast, the prior consumption of caffeine has been shown to augment the magnitude of the symptomatic response to moderate hypoglycaemia in non-diabetic [Kerr et al, 1993a] and in diabetic subjects [Debrah et al, 1996]. Although it has been claimed that the frequent ingestion of caffeine may have a therapeutic application to improve symptomatic awareness in people with impaired awareness of hypoglycaemia, this would require further study before widespread application in people with diabetes [Watson et al, 2000].

Beta-adrenoceptor antagonists have been shown to blunt specific autonomic symptoms of hypoglycaemia, though sweating is either unaltered [Macdonald et al, 1982] or may even be increased [Molnar & Read, 1974, Clausen Sjobom et al, 1987, Kerr et al, 1990a, Hirsch et al, 1991b]. The peripheral vasoconstriction caused by beta-adrenoceptor antagonists may diminish the sensation of warmth [Kerr et al, 1990a]. When these medications are prescribed to people with insulin-treated diabetes, they should be made aware of this potential change in symptomatology, but should not preclude their use. Although the beta agonist, terbutaline, [Saleh & Cryer, 1997] and the methylxanthine, theophylline [Hvidberg et al, 1994] augment counterregulation and speed recovery from hypoglycaemia, their effects on the symptomatic response to hypoglycaemia have not been evaluated.



### **1.5.7 Altered ability to detect symptoms**

#### *Anticipation*

People with diabetes who anticipate the possible development of hypoglycaemia because of a missed meal or strenuous exercise usually focus their attention on the development of symptoms and are therefore more likely to detect the onset of hypoglycaemia [Cox et al, 1993a]. Knowledge of the imminence of experimentally-induced hypoglycaemia in non-diabetic subjects enhanced the intensity of neuroglycopenic, but not autonomic, symptoms [Pohl et al, 1997], demonstrating the effect of anticipation on the perception of symptoms.

#### *Circumstances*

Circumstances and activities are also important. For example, individuals requiring manual dexterity for their work, such as an artist, may be more sensitive to noticing tremor. Neuroglycopenic symptoms such as difficulty in concentrating may be recognised more readily by individuals who are occupied with active mental activity. The converse applies to the effects of distraction reducing the perception (or awareness) of hypoglycaemia. An activity associated with similar symptoms may alter their perception or interpretation in the context of simultaneously occurring hypoglycaemia. For example, while sweating is an appropriate response during physical activity, on a hot day it may be ignored, and be of less benefit to alert the individual developing hypoglycaemia.

#### *Altered ability to detect low blood glucose*

Because many of the common symptoms of hypoglycaemia can be attributed to alternative physiological causes, some of which may also promote a fall in blood glucose (such as exercise-induced sweating, pounding heart and fatigue), people with diabetes must be familiar with the symptoms of hypoglycaemia that are peculiar to themselves. Previous experience of hypoglycaemia symptoms is necessary to permit their early detection and correct interpretation. However, asymptomatic biochemical hypoglycaemia is common in people treated with

insulin [Dornan et al, 1981, Arias et al, 1985], and a lack of correlation has been observed between actual blood glucose concentration and the subjective symptomatic response [Pramming et al, 1990]. This reinforces the need for frequent measurement of blood glucose using an accurate blood glucose meter.

#### **1.5.8 Plasma insulin concentration and method of delivery**

At comparable levels of hypoglycaemia, plasma catecholamine concentrations appear to be higher with greater levels of hyperinsulinaemia. Therefore, it could be assumed that the higher plasma catecholamine concentrations indicated more intense stimulation of the autonomic nervous system. Two studies, both in people with type 1 diabetes, have examined this effect on hypoglycaemia symptoms.

Using the glucose clamp technique and different concentrations of plasma insulin, the symptoms of trembling, sweating, facial flushing and hunger during hypoglycaemia (arterialised blood glucose 2.8 mmol/l) were found to be attenuated when plasma insulin concentrations were high [Kerr et al, 1991a]. Only hunger was affected during more profound hypoglycaemia (blood glucose 2.2 mmol/l), suggesting that this effect of hyperinsulinaemia may be manifest only during moderate degrees of hypoglycaemia. By contrast, during higher plasma insulin concentrations, Lingenfelser and colleagues (1996) observed an increased magnitude of autonomic and neuroglycopenic symptoms. The relevance of these discordant results to clinical practice is difficult to assess, but the suggestion that hyperinsulinaemia may provoke more profound hypoglycaemic symptoms during an equivalent hypoglycaemic stimulus is of interest and may be relevant to the lower frequencies of hypoglycaemia that have been described with the use of fast-acting insulin analogues, with which a higher post-injection peak of plasma insulin is achieved.

Insulin species (animal versus human) has been proposed to be a modifier of the symptoms of hypoglycaemia. A small number of patients reported a change in

their ability to perceive the onset of hypoglycaemia and in the nature of their symptoms of hypoglycaemia after changing from animal to human species of insulin in the 1980s. However, despite extensive investigation little scientific evidence has emerged to support these claims other than a few subjective and anecdotal reports, and most comparative, controlled trials have produced negative results [Nelleman Jorgensen et al, 1994, Airey et al, 2000]. Some of the patients' observations may be explained by the altered pharmacokinetics of human insulin and by advancing knowledge about the mechanisms of impaired awareness of hypoglycaemia. However, human insulin does not suit some people who do not find this a satisfactory form of therapy, and animal insulin species should remain available indefinitely.

### **1.5.9 Recommended clinical assessment of symptoms**

Because of the effects of time and extraneous factors on hypoglycaemia symptomatology, the symptoms experienced by patients with insulin-treated diabetes should be reviewed at least annually and should certainly be discussed at the diabetes clinic visit. The diabetes team may find value in having a proforma sheet of the questions to ask about symptoms of hypoglycaemia so enabling a comprehensive review with some degree of standardisation, which could allow for effective audit. A detailed documentation of symptoms is also useful when advising people on medical fitness to drive, to track changes in awareness of hypoglycaemia, in situations with medico-legal import, and for clinical research.

If biochemical hypoglycaemia is a frequent occurrence, patients should be advised to make a note of the concomitant symptoms that they have experienced. Similarly, patients should try to identify whether these symptoms occur when their blood glucose is not low. Through these measures they will identify their relevant sensitive and specific symptoms of hypoglycaemia.

## **1.6 ACQUIRED HYPOGLYCAEMIA SYNDROMES IN TYPE 1 DIABETES**

In people with diabetes, glycaemic thresholds can be modified by the prevailing glycaemic state, particularly by strict control and can also be influenced by metabolic change such as antecedent hypoglycaemia. Many studies in people with insulin-treated diabetes who have strict glycaemic control have demonstrated that the counterregulatory hormonal and symptomatic responses to hypoglycaemia do not occur until a much lower blood glucose concentration is reached, particularly when the glycated haemoglobin concentration is within the non-diabetic range [Amiel, 1999]. Similarly, antecedent hypoglycaemia persisting for one hour or more has been shown to diminish the magnitude of the symptomatic and neuroendocrine responses to any subsequent episode of hypoglycaemia occurring within the subsequent 24 to 48 hours [Frier & Fisher, 1999]. During periods of strict glycaemic control the cerebral uptake of glucose is maintained during hypoglycaemia so preserving cognitive function despite a low blood glucose [Boyle et al, 1995]. This is a manifestation of cerebral adaptation to prolonged exposure to neuroglycopenia, but it is maladaptive as the early symptomatic warning to hypoglycaemia is absent, risking progression to severe neuroglycopenia.

### **1.6.1 Counterregulatory deficiencies**

In many people with type 1 diabetes, the glucagon secretory response to hypoglycaemia becomes diminished or absent within a few years of the onset of insulin-deficient diabetes. With glucagon deficiency alone, blood glucose recovery from hypoglycaemia is relatively unaffected because counterregulation is maintained by the actions of adrenaline. However, in up to 45% of people who have type 1 diabetes of long duration there is impairment of the secretion of glucagon and adrenaline [Gerich & Bolli, 1993], predisposing them to serious deficiencies of glucose counterregulation when exposed to hypoglycaemia, delaying the recovery of blood glucose and allowing progression to more severe hypoglycaemia. The dual impairment of glucagon and adrenaline responses results in the syndrome of defective glucose counterregulation. People with

type 1 diabetes of long duration are therefore at increased risk of developing severe and prolonged hypoglycaemia, particularly when intensive insulin therapy is used [White et al, 1983]. Indeed, people with type 1 diabetes and combined deficiencies of their glucagon and adrenaline responses to hypoglycaemia have been shown to be at 25-fold or even higher increased risk for severe iatrogenic hypoglycaemia during intensive insulin therapy compared with those with absent glucagon but retention of adrenaline responses [White et al, 1983, Bolli et al, 1984].

### **1.6.2 Impaired awareness of hypoglycaemia**

This occurs when the symptomatic warning is diminished or inadequate in people with diabetes. Several mechanisms underlying this problem have been proposed (table 1.3). Impaired awareness of hypoglycaemia is generally thought to be due to reduced sympathoadrenal responses and the resultant reduced, largely adrenergic symptom response, to a given level of hypoglycaemia [Cryer, 2002, Grimaldi et al, 1990, Clarke et al, 1991, Hepburn et al, 1991].

Impaired awareness of hypoglycaemia is common, affecting almost 25% of all insulin-treated patients, and becomes more prevalent with increasing duration of diabetes [Frier & Fisher, 1999]. Because it compromises behavioural defences against developing hypoglycaemia, e.g. food ingestion, impaired awareness of hypoglycaemia predisposes the patient to a high risk of developing severe hypoglycaemia [Gold et al, 1994]. In some patients, impaired awareness may be reversible, being attributable to an elevated glycaemic threshold during intensive insulin therapy or has followed recurrent severe hypoglycaemia [Cryer et al, 1994] but, in patients with type 1 diabetes of long duration, it may be permanent.



### **1.6.3 Central autonomic failure**

Because hormonal counterregulatory deficiencies and impaired awareness of hypoglycaemia co-segregate and are associated with an increased frequency of severe hypoglycaemia, the concept of a “hypoglycaemia-associated autonomic failure”, or HAAF, has been proposed by Cryer [1992] who has speculated that recurrent severe hypoglycaemia may be the primary problem which causes these abnormalities and by establishing a vicious circle has maintained this state. This concept deems that recent antecedent hypoglycaemia, in those with type 1 diabetes and advanced type 2 diabetes, causes defective glucose counterregulation through a reduced adrenaline response to subsequent hypoglycaemia in the setting of an absent glucagon response, and impaired awareness of hypoglycaemia by reducing the sympatho-adrenal response and thus resulting autonomic symptom response to subsequent hypoglycaemia.

**Table 1.3** Possible mechanisms of impaired awareness of hypoglycaemia

<b>Mechanism</b>	<b>Study</b>
Strict glycaemic control	Clarke et al, 1991 Kinsley et al, 1995 Boyle et al, 1995 Lager et al, 1986 Amiel et al, 1988 Maran et al, 1995 Davis & Shamoon, 1991
Insulinoma in non-diabetic patients	Mitrakou et al 1993
Antecedent hypoglycaemia	Davis et al, 1992 Dagago-Jack et al, 1993 Lingenfelser et al, 1993 George et al, 1995 Ovalle et al, 1998 Fanelli et al, 1998
Counterregulatory deficiency	Gerich et al, 1973 White et al, 1983 Bolli et al, 1988 Hirsch & Shamoon, 1987 Dagago-Jack et al, 1993
Hypoglycaemia-associated central autonomic failure	Cryer, 1992 Davis et al, 1996 Davis et al, 1997 McGregor et al, 2002



## 1.7 RISK FACTORS FOR SEVERE HYPOGLYCAEMIA

An essential prerequisite for hypoglycaemia is hyperinsulinaemia. Absolute or relative insulin excess occurs when:

- a. Insulin or an insulin secretagogue dose is excessive, badly timed or of the wrong type.
- b. Exogenous glucose delivery is decreased, e.g. a missed meal or overnight fast.
- c. Endogenous glucose production is decreased, e.g. following alcohol.
- d. Glucose utilisation is increased, e.g. during and after exercise.
- e. Insulin sensitivity is increased, e.g. late after exercise, following weight loss, improved fitness.
- f. Insulin clearance is decreased, e.g. in renal failure.

However, by relying on the above factors alone, it is often difficult to account for an episode of hypoglycaemia. To understand this requires an appreciation of the limitations of existing treatments for type 1 diabetes in combination with the acquired syndromes of hypoglycaemia. As previously noted, the insulin preparations in current use do not replicate the physiological changes in plasma insulin concentrations that occur in non-diabetic individuals. Therefore, it is likely that most people with type 1 diabetes will encounter significant hyperinsulinaemia at many points during the day and night, but they do not always experience hypoglycaemia at these points, especially towards the start of their diabetes career. This is because the integrity of the physiological and behavioural defences against a falling plasma glucose concentration determines if less marked hyperinsulinaemia causes an episode of hypoglycaemia. Thus, it is easier to account for hypoglycaemia in the setting of absolute or relative insulin excess plus compromised glucose counterregulation [Cryer et al, 1994]. Risk factors relevant to compromised glucose counterregulation are outlined in table 1.4. These factors are markers of the key features of the pathophysiology of glucose counterregulation discussed earlier. For example, by successfully

achieving strict glycaemic control, with a glycated haemoglobin within the normal range, people with type 1 diabetes have a higher chance of developing low blood glucose concentrations. Recovery from subsequent hypoglycaemia may be compromised by the effect on modifying glycaemic thresholds for counterregulatory hormone secretion, so causing more hypoglycaemia. Similarly, a history of severe hypoglycaemia indicates recent antecedent hypoglycaemia, and an increase in the glycaemic threshold for the symptomatic and neuroendocrine responses to a low, and falling, plasma glucose concentration [Cryer et al, 1994].

## **1.8 MORBIDITY AND MORTALITY OF SEVERE HYPOGLYCAEMIA**

An episode of acute hypoglycaemia is, at the very least, a nuisance and a distraction. However, for the person with type 1 diabetes, hypoglycaemia can exert a profound social, psychological and physical burden and, in its most extreme form, can result in death.

### **1.8.1 Morbidity of hypoglycaemia**

In a group of 60 people with type 1 diabetes, 11 described severe hypoglycaemia as being the most frightening event in their lives [Sanders et al, 1975]. Pramming et al [1991] found that although most people with diabetes were unconcerned about episodes of mild hypoglycaemia, they expressed an equal degree of anxiety about exposure to severe hypoglycaemia as to the development of late diabetic complications, such as blindness or renal failure. Perhaps unsurprisingly, some people with diabetes avoid the attainment of good glycaemic control to prevent hypoglycaemia [Cox et al, 1987].

Physical injury can occur and is sometimes serious. Fractures of long bones, joint dislocations, soft tissue injuries, head injuries and occasionally burns have been described as a direct consequence of accidents associated with hypoglycaemia [Hepburn et al, 1989]. Hypothermia may also be a direct consequence of hypoglycaemic coma. In a report of 102 cases of

**Table 1.4** Risk factors for severe hypoglycaemia

<b>Risk factor</b>	<b>Study</b>
Intensive insulin therapy	The DCCT, 1991
Strict glycaemic control/low HbA1c	The DCCT, 1991 Allen et al, 2001
Long duration of diabetes	The DCCT, 1991 Bott et al, 1997
Younger age	The DCCT, 1991 Bott et al, 1997
Male	The DCCT, 1991
History of severe hypoglycaemia	The DCCT, 1991 Bott et al, 1997 Muhlhauser et al, 1998
History of impaired awareness of hypoglycaemia	Gold et al, 1994 MacLeod et al, 1994a Clarke et al, 1995 Muhlhauser et al, 1998
C-peptide negative	The DCCT, 1991 Bott et al, 1997 Muhlhauser et al, 1998
High total daily insulin dose	The DCCT, 1991 Bott et al, 1997 ter Braak et al, 2000
Sleep	The DCCT, 1991 Jones et al, 1998 Banarer and Cryer, 2003
Exercise	Galassetti et al, 2001 McGregor et al, 2002
Alcohol	Arky et al, 1968 Feher et al, 1989 ter Braak et al, 2000
Social class	Muhlhauser et al, 1998
Renal impairment	Muhlhauser et al, 1991
High s-ACE activity	Pedersen-Bjorgaard U et al, 2001 Pedersen-Bjorgaard U et al, 2003 Nordfeldt S et al, 2003

hypoglycaemic coma induced either by insulin or by glibenclamide, physical injury was reported in seven patients, myocardial ischaemia in two and stroke in one patient [Ben-Ami et al, 1999]. In addition to the unpleasant symptoms of hypoglycaemia such as palpitations, anxiety, shaking and sweating, acute hypoglycaemia triggers a profound haemodynamic response secondary to sympatho-adrenal activation and the secretion of adrenaline, causing an increase in the workload of the heart and a widening of pulse pressure [Fisher & Heller, 1999]. Although this degree of haemodynamic stress is unlikely to cause any difficulties in the young person with normal cardiac function, in the older individual with diabetes who may have underlying cardiovascular disease, hypoglycaemia may have serious consequences. In diabetic patients who have ischaemic heart disease, cardiac arrhythmias may be induced. These have been described during experimentally-induced hypoglycaemia and in anecdotal case reports, with atrial fibrillation and premature atrial and ventricular contractions all being observed during hypoglycaemia in diabetic patients who had no overt clinical evidence of heart disease [Lindström et al, 1992, Fisher & Heller, 1999]. Sudden death during hypoglycaemia-induced cardiac arrhythmia has been described in individual case reports [Frier et al, 1995, Burke & Kearney, 1999]. Transient ventricular tachycardia has been observed during experimental hypoglycaemia in a non-diabetic subject with coronary heart disease and myocardial infarction has also been reported in association with acute hypoglycaemia [Fisher & Heller, 1999]. Acute hypoglycaemia can lengthen the QT interval on the electrocardiogram both in non-diabetic humans and people with diabetes [Marques et al, 1997]. When combined with the effects of catecholamine-mediated hypokalaemia and the profound haemodynamic changes associated with acute hypoglycaemia, the potential for inducing a serious cardiac arrhythmia may be increased.

An array of psychological and neurological manifestations of acute hypoglycaemia can cause loss of sensory and motor functions. Transient ischaemic attacks and transient hemiplegia may be a feature of neuroglycopenia

and supports the justification for blood glucose testing of patients in coma or with suspected stroke. Less commonly, permanent neurological deficits have been described, especially in elderly patients. These are probably caused by mechanisms such as direct focal cerebral damage from glucopenia, acute thrombotic occlusion secondary to the haemodynamic and haematological effects of hypoglycaemia or by cerebral ischaemia provoked by changes in regional blood flow in the brain [Perros & Deary, 1999]. It is unusual for severe hypoglycaemia to cause permanent brain damage but this may arise if the episode is protracted and often occurs in the context of excessive insulin dosage, deliberate or accidental, and with excessive alcohol consumption [Agardh et al, 1983].

### **1.8.2 Mortality of hypoglycaemia**

Hypoglycaemia is a relatively rare cause of death in people with type 1 diabetes. In a study by the British Diabetic Association (now Diabetes UK), an estimated 4% of deaths in men with type 1 diabetes aged 20 to 49 years and 1% of deaths in women in the same age group were attributed to hypoglycaemia [Laing et al, 1999]. Occasional deaths in otherwise healthy young people have been referred to as the 'dead in bed syndrome' with the most likely cause being hypoglycaemic-induced cardiac arrhythmias [Tattersall & Gill, 1991].

## **1.9 REDUCING THE FREQUENCY OF SEVERE HYPOGLYCAEMIA**

Reducing the risk of hypoglycaemia, while maintaining good glycaemic control is difficult but can be achieved. Firstly, the issue of hypoglycaemia has to be addressed frequently, preferably at every contact with the diabetes team. Unfortunately, this first principle is often neglected in the modern diabetes care setting, which increasingly concentrates on the cardiovascular risk profile of patients with type 2 diabetes. Secondly, the principles of good diabetes care need to be applied, including patient education and empowerment, frequent home blood glucose monitoring, appropriate use of insulin, the setting of



individual glycaemic goals, and ongoing guidance and support. Finally, the conventional risk factors for hypoglycaemia have to be taken into consideration in addition to those indicative of counterregulatory failure in the individual with diabetes.

### **1.9.1 Raising the issue of hypoglycaemia**

Hypoglycaemia cannot be dealt with if it remains unrecognised, so the person with diabetes should always be asked if hypoglycaemia is occurring. Are they aware of hypoglycaemia and at what blood glucose concentration do they experience symptoms? Do they have asymptomatic biochemical hypoglycaemia and have there been any severe episodes? What is the temporal relation to meals and snacks, alcohol ingestion and exercise? Is nocturnal hypoglycaemia a problem? It is particularly important to ensure that both the doctor and the patient understand what is meant by hypoglycaemia (see section 1.2).

### **1.9.2 Principles of good diabetes care**

A well informed patient will understand the pharmacokinetics of the insulin that they are using and the impact of food, alcohol and exercise on their home blood glucose monitoring. They will be competent in responding to the latter, whether it is a high or a low blood glucose reading, and will take appropriate remedial action. Although no trials have demonstrated that the use of home blood glucose monitoring (HBGM) reduces the risk of severe hypoglycaemia, patients will recognise patterns of HBGM, which can predict who is at increased risk of severe hypoglycaemia [Cox et al, 1994b], allowing appropriate adjustment of therapy.

If frequent or troublesome hypoglycaemia is problematical, the insulin regimen may require adjustment. For example, a fixed mixture of insulin often causes unwanted nocturnal hyperinsulinaemia, predisposing to unrecognised hypoglycaemia. When isophane insulin is administered before the evening meal, nocturnal hypoglycaemia often occurs around 3.00-4.00 am [Pramming et

al, 1985], while soluble insulin before a late evening meal can cause hypoglycaemia in the early hours of the night [Vervoort et al, 1996]. Therefore, nocturnal hypoglycaemia may induce impaired awareness of hypoglycaemia through the pathogenetic mechanism of antecedent hypoglycaemia [Veneman et al, 1993, Fanelli et al, 1998]. To avoid nocturnal hypoglycaemia useful therapeutic manoeuvres include the use of a rapid-acting insulin analogue before the evening meal [Brunelle et al, 1998, Home et al, 1998, Heller et al, 1999] or the evening dose of isophane insulin can be deferred at bedtime.

If impaired awareness of symptoms is related to strict glycaemic control, the glycaemic control can be relaxed by reducing the total prescribed dose of insulin. Three studies have demonstrated an improvement in symptoms of hypoglycaemia following scrupulous avoidance of hypoglycaemia in a small number of patients over periods of three weeks to one year [Cranston et al, 1994, Fanelli et al, 1994a, Dagogo-Jack et al, 1994]. In two of the studies [Cranston et al, 1994, Fanelli et al, 1994a,], the definition of impaired awareness of hypoglycaemia was based upon an increased frequency of asymptomatic biochemical hypoglycaemia, as opposed to a history of loss of awareness of hypoglycaemia. A small rise in HbA1c occurred in all three studies, so that part of the response may have been confounded by relaxation of glycaemic control. In another study, avoidance of hypoglycaemia restored some of the counterregulatory deficiencies, but not the symptomatic response to hypoglycaemia [Davis et al, 1994]. When continuous subcutaneous insulin infusion was used to deliver insulin overnight instead of bedtime isophane insulin, the intensity of the warning symptoms of hypoglycaemia was enhanced, perhaps as a result of reducing the frequency of asymptomatic nocturnal hypoglycaemia [Kanc et al, 1998]. Although avoidance of hypoglycaemia is clearly desirable, it requires intensive efforts on behalf of both the patient and their healthcare providers, and is often difficult to achieve.



In a patient treated with a basal-bolus regimen, morning fasting hypoglycaemia indicates that the basal insulin requires adjustment; daytime hypoglycaemia requires modification of the bolus insulin. Substitution of a long-acting insulin analogue (insulin glargine or insulin detemir) for isophane insulin, may also reduce the frequency of hypoglycaemia, both nocturnal [Vague et al, 2003, Ratner et al, 2000] and severe hypoglycaemia [Ratner et al, 2000]. Blood Glucose Awareness Training (BGAT) has been developed in the USA as a method of teaching people who have type 1 diabetes with impaired awareness of hypoglycaemia how to recognise, and distinguish between, high and low blood glucose concentrations by detecting and interpreting subtle symptomatic changes [Cox et al, 1989]. BGAT does appear to improve the accuracy of blood glucose estimation in people with type 1 diabetes and may reduce the frequency of undetected hypoglycaemia [Cox et al, 1995]. Although potentially valuable, this programme has significant resource and cost implications.

### **1.9.3 Risk factors for hypoglycaemia and compromised glucose counterregulation**

It is important to consider the risk factors that lead to absolute or relative insulin excess discussed earlier. These include excessive insulin dose, inappropriate timing of insulin, and the wrong insulin being administered. The effects of food and alcohol need taken into account and patients educated about the need for regular meals and snacks and about the adjustment of carbohydrate intake and insulin dose before and after exercise. In addition, risk factors for compromised glucose counterregulation should be sought. Therefore, a diagnosis of impaired awareness of hypoglycaemia, which is usually evident from the history, implies defective counterregulation and a history of recurrent hypoglycaemia. If the latter is not apparent to the patient or their family, and is not reflected in the patient's HBGM, then it is most likely occurring during the night.

As noted earlier, nocturnal hypoglycaemia is common and is likely due to a combination of the imperfect pharmacokinetics of the available insulins in current use and the effects of sleep on the recognition of warning symptoms and

reduced adrenaline response to hypoglycaemia [Jones et al, 1998]. The frequency of nocturnal hypoglycaemia may be reduced by the ingestion of a bedtime snack, but the efficacy of this is limited to the first half of the night [Saleh & Cryer, 1997]. Other experimental approaches have included the bedtime administration of the amino acid alanine, which stimulates glucagon release, and the  $\beta_2$  adrenergic agonist, terbutaline [Saleh & Cryer, 1997]. Furthermore, uncooked cornstarch is slowly digested and may maintain blood glucose concentrations for several hours [Kaufman & Devgan, 1996]. Finally, the frequency of nocturnal hypoglycaemia can be reduced by adjustment of the insulin regimen as noted earlier, e.g. the use of a rapid acting analogue with the evening meal or a long-acting basal analogue at bedtime. The evidence for the reduction in the frequency of hypoglycaemia with the rapid-acting analogue, insulin lispro, will now be examined.

#### **1.9.4 Insulin analogues**

When insulin exists as a dilute solution and is in the circulation, it is in the form of a monomer. In concentrated solution and in crystalline form as in pharmaceutical preparations prepared for parenteral administration, six monomers self-associate with two zinc ions to form a hexamer. This structure affects the pharmacokinetics of insulin because its absorption into the circulation from subcutaneous injection sites requires the monomeric form, and the slow absorption of insulin from subcutaneous tissue is partly caused by the time taken for the dissociation and dispersal of insulin.

The introduction of recombinant DNA technology for protein synthesis which permitted the development of human insulin in the 1980s was followed by the ability to manipulate various amino acid sequences of the A and B chains of the insulin molecule, and so modify the absorption characteristics of the hormone. This led to the development of insulin analogues which have differing durations of action and rapidity of onset.

### *Insulin lispro*

The first monomeric insulin to be introduced for clinical use was insulin lispro (Humalog, Eli Lilly & Co), which is formed by reversal of the amino acids lysine and proline, at positions 28 and 29 on the insulin B chain. This reversal weakens the binding of dimers and hexamers, allowing rapid dissociation into the monomeric form following subcutaneous injection. Insulin lispro is therefore absorbed quickly, has a rapid onset of action (10 to 20 mins), an earlier peak effect (1 to 2 hours), and a shorter duration of activity (3 to 5 hours), than soluble (regular) insulin. The rapid absorption of insulin lispro allows this insulin to be administered immediately before a meal. The overall bioavailability (~ 99%) of insulin lispro is similar to human soluble insulin [Radziuk et al, 1997].

### *Insulin lispro and hypoglycaemia*

Lower frequencies of mild (self-treated) symptomatic, biochemical, nocturnal and severe (requiring assistance) hypoglycaemia have been recorded in people with diabetes treated with insulin lispro, compared with human soluble insulin. For example, in a prospective six-month, multicentre study of 1008 adults with type 1 diabetes, the administration of insulin lispro immediately before meals was compared with human soluble (regular) insulin, injected 30 to 45 minutes before meals [Anderson et al, 1997]. The frequency of symptomatic and biochemical hypoglycaemia was 12% lower with insulin lispro and this effect was particularly beneficial overnight. A cumulative meta-analysis of eight studies, comprising 2576 patients with type 1 diabetes, demonstrated that severe hypoglycaemia (defined as coma or an episode requiring treatment with parenteral glucose or glucagon) was 30% lower with insulin lispro than with soluble (regular) insulin [Brunelle et al, 1998].

In a multicentre study in the UK of 135 subjects with type 1 diabetes, insulin lispro was compared with human soluble (regular) insulin given before meals, with isophane (NPH) being administered at bedtime in both regimens. Over a

four month period, strict glycaemic control was achieved with both treatments, with mean glycated haemoglobin concentrations of around 6.0% [Heller et al, 1999]. Episodes of mild symptomatic and biochemical hypoglycaemia occurred less frequently with insulin lispro, although the main beneficial effect in minimising hypoglycaemia was predominantly during the night.

The potential benefit of using insulin lispro before the evening meal to reduce the risk of nocturnal hypoglycaemia is based on the short duration of action of this insulin, in that its hypoglycaemic action wanes by bedtime, so reducing the level of nocturnal hyperinsulinaemia. This was demonstrated in a double-blind, crossover study comparing insulin lispro with human soluble (regular) insulin in a group of 14 adolescents with type 1 diabetes [Mohn et al, 1999], and in adults with type 1 diabetes [Ahmed et al, 1998]. In both studies the overnight profiles showed that insulin lispro was associated with lower plasma insulin and higher blood glucose concentrations, and in the adult group a lower frequency of nocturnal hypoglycaemia was observed [Ahmed et al, 1998].

Impaired awareness of hypoglycaemia is a common acquired complication of insulin therapy in type 1 diabetes, and is associated with a sixfold higher frequency of severe hypoglycaemia than in individuals with normal awareness [Gold et al, 1994]. In a study in Edinburgh, 33 subjects with type 1 diabetes of long duration and co-existing impaired awareness of hypoglycaemia, participated in a prospective crossover trial for 12 months, in which the use of insulin lispro was compared with human soluble (regular) insulin [Ferguson et al 2001]. No difference in glycaemic control was observed between the two groups but a trend to a lower incidence of severe hypoglycaemia was evident in the group treated with insulin lispro (55 versus 88 episodes;  $p=0.087$ ). This was also associated with a lower incidence predominantly of nocturnal hypoglycaemia (25 versus 47 episodes) [Ferguson et al 2001].



The recommended time of administration of insulin lispro is immediately before a meal, to restrict the postprandial rise in blood glucose. However, when a meal has a high fat content (particularly fat in the solid-phase), the rate of gastric emptying is reduced [Horowitz et al, 1991] and the absorption of glucose is slower. In addition, gastric emptying is attenuated in many people with type 1 diabetes of long duration, in whom it may be preferable to administer insulin lispro after the meal to provide a closer match between the time-action profile of the fast-acting insulin and the slower postprandial rise in blood glucose. This modification does minimise the risk of postprandial hypoglycaemia [Burge et al, 1997, Schernthaner et al, 1998, Strachan & Frier, 1998]. Fast-acting insulin analogues should be used with caution in people with overt autonomic neuropathy, particularly those with a history of gastroparesis, where delayed gastric emptying enhances the risk of postprandial hypoglycaemia. The flexibility in time of injection of insulin lispro may be of benefit during intercurrent illness and in situations where the quantity of food to be ingested may be unpredictable, as in the routine management of very young children with diabetes, or where the content and timing of meals may be unknown in advance, e.g. meals on airline flights. Because of the rapid onset of action of insulin lispro, the risk of early postprandial hypoglycaemia is increased by exercise; appropriate reduction of the pre-meal dose of insulin lispro may have to be made if postprandial exercise is contemplated [Tuominen et al, 1995].

### **1.10 Summary**

Iatrogenic hypoglycaemia is a common problem for people with type 1 diabetes. Despite the efforts of healthcare staff and patients to minimise the frequency of hypoglycaemia, the problem persists because, in general, the aim of treatment is strict glycaemic control. Even with optimal insulin therapy, some people with diabetes will suffer from recurrent severe hypoglycaemia which leads to significant disruption of their lives. Because of this, hypoglycaemia precludes the maintenance of euglycaemia in people with type 1 diabetes and exposes them to the risks of hyperglycaemia.

**CHAPTER 2**

**EFFECTS OF ACUTE HYPOGLYCAEMIA ON COGNITIVE  
FUNCTION**

### **2.1.1 Introduction**

The function of the human brain depends upon the adequate delivery of glucose as a metabolic fuel. Consequently, when the glucose concentration of the blood is insufficient to meet the metabolic requirements of the brain, its function deteriorates. Therefore, in addition to the study of the neuroendocrine responses to hypoglycaemia, several investigators have examined the effect of low blood glucose concentration on brain function. This has been done in various ways; in addition to administering tests of cognitive function, some have examined the neuroglycopenic symptoms generated during hypoglycaemia, whereas others have applied electrophysiological measures such as brain-evoked potentials.

### **2.1.2 Studies of cognitive function during acute hypoglycaemia**

Although the dramatic effects of severe hypoglycaemia were recognised soon after the discovery of insulin [Banting et al, 1923], it was not until much later that there was a systematic study with the use of neuropsychological testing. In one of the first studies, Russell & Rix-Trot [1975] examined cognitive function during insulin-induced hypoglycaemia in thirteen subjects with suspected pituitary disease. An intravenous bolus of insulin was administered to lower the mean blood glucose to 1.6 mmol/l and tests of cognitive function were compared with those found during euglycaemia. This indicated that fine motor coordination, word recall and concentration were impaired during hypoglycaemia [Russell & Rix- Trot, 1975].

A subsequent study by Flender & Lifshitz [1976] utilised the glucose tolerance test in eight children, both with and without diabetes. In that study, fine motor coordination, memory and concentration were impaired at blood glucose concentrations between 2.9 and 3.6 mmol/l. However, these studies were not controlled and involved a rapid change and instability in the blood glucose, thus making it difficult to reach any firm conclusions other than that cognitive disruption was evident.



These difficulties were overcome by Holmes and her colleagues in a series of studies in the 1980s. They utilised a glucose-controlled insulin infusion system as a crude artificial pancreas to maintain blood glucose concentrations at low, normal or high levels in subjects with type 1 diabetes. This permitted an examination of various aspects of cognitive function during hypoglycaemia. The level of hypoglycaemia achieved in these studies was mild, ranging from 3.1 to 3.3 mmol/l. Visual and auditory reaction times were prolonged during hypoglycaemia [Holmes et al, 1983], there was a slowing of mental arithmetic tests [Holmes et al, 1983], verbal fluency was impaired [Holmes et al, 1984], and there was impaired generation of colour-name associations [Holmes et al, 1984]. In a further study by Holmes and her colleagues, it was demonstrated that simple motor and sensory skills were not affected by hypoglycaemia in contrast to more complicated discrimination tests and choice reaction time where a decision had to be made [Holmes et al, 1986].

Pramming et al [1986] infused insulin intravenously in 16 subjects with type 1 diabetes to progressively lower the blood glucose concentration from 6.0 to 3.0 mmol/l, and then 2.0 mmol/l followed by a return of the blood glucose to 6.0 mmol/l, with a stable blood glucose plateau between each level. They administered a variety of psychological tests including trail making B, finger tapping, digit span, story recall and serial events, thus covering a wide range of cognitive modalities. When the tests were scored, the results were presented as a summation of all the cognitive tests administered. Three quarters of the subjects deteriorated when the blood glucose was lowered from 6.0 mmol/l to 3.0 mmol/l. Most of the participants deteriorated in performance between 3.0 and 2.0 mmol/l and they all improved when the blood glucose was returned to 6.0 mmol/l [Pramming et al, 1986].

Therefore, it was clear from these early studies that cognitive function is impaired during acute hypoglycaemia. Since then a large number of studies have demonstrated that moderate hypoglycaemia (2.0-3.0 mmol/l) impairs brain

function, and the data from these studies has allowed reviewers to reach a number of conclusions.

Firstly, many aspects of cognitive function, such as the performance of tests that require attention, concentration, psychomotor skill, the accessing of longterm memory and the ability to ignore distracting information, decline as the blood glucose concentration drops below around 3.0 mmol/l [Deary, 1993b]. It has been noted that more profound hypoglycaemia causes a greater cognitive impairment and that in health, a protective hierarchy exists whereby the counterregulatory responses and symptoms of hypoglycaemia occur before the onset of cognitive dysfunction [Schwartz et al, 1987, Mitrakou et al, 1991, Fanelli et al, 1994].

Secondly, cognitive tasks are more likely to be disrupted at a given level of neuroglycopenia than are simpler motor tasks. Pramming et al [1986] demonstrated that moderate hypoglycaemia of 2.0 mmol/l had no effect on a simple motor task (finger tapping), whereas more complex tests, like trail making B became impaired. In the study by Cox et al [1993b], 10 subjects with type 1 diabetes were administered the Paced Auditory Serial Addition Test (PASAT) to assess cognitive function, and the Finger Tapping Test (FTT) to assess motor function, during euglycaemia and hypoglycaemia. At a blood glucose nadir of 2.6 mmol/l only the PASAT was disrupted [Cox et al, 1993b].

Thirdly, there is considerable inter-individual variability in the blood glucose concentration at which brain function becomes disrupted. Widom and Simonson [1990] demonstrated that some individuals had significant decline in performance at blood glucose concentrations of 4.0 mmol/l, whereas others were functioning normally at 2.2 mmol/l. In the study of reaction time by Herold et al [1985], 14 non-diabetic volunteers and 12 subjects with type 1 diabetes were examined at a blood glucose concentration of 2.5 mmol/l. Whereas some subjects showed marked prolongation of reaction times, others had small

increases, a few showed no change, and some even improved during hypoglycaemia.

Other investigators have observed that accuracy is often spared at the expense of speed during hypoglycaemia. Many tests that involve speeded responses and are more cognitively complex become impaired during hypoglycaemia. In the study of 17 subjects with type 1 diabetes by Widom and Simonson [1990], demanding tasks like letter cancellation, Digit Symbol Substitution Test (DSST) and trail making were impaired at arterialised blood glucose concentrations of 2.4 to 2.8 mmol/l, whereas digit span and word recall remained unaffected.

Lastly, an important practical point for the person with diabetes is that the recovery of cognitive function does not occur immediately on restoration of euglycaemia. Several studies have reported delays of 45 to 90 minutes for mental performance or electrophysiological parameters to return to normal after a period of hypoglycaemia [Blackman et al, 1992, Lindgren et al 1996]. Recent studies with a more robust methodology have demonstrated residual cognitive impairment at 20 minutes [Evans et al, 2000] and 60 minutes [Fanelli et al, 2003] following restoration of euglycaemia. In a clinical study, Strachan and colleagues examined 20 subjects with insulin-treated diabetes who had experienced an episode of severe hypoglycaemia, and administered cognitive tests at 1.5, 9 and 30 days after the event, comparing them with a group of matched controls. Only one test from a large battery showed continuing dysfunction after 1.5 days, therefore it is unlikely that severe hypoglycaemia impairs acute mental capacity by more than 36 hours [Strachan et al, 2000].

Table 2.1 summarises the key facts that are evident regarding cognitive disruption during acute insulin-induced hypoglycaemia.

**Table 2.1** Key facts derived from studies of acute hypoglycaemia and cognitive function

<b>Cognitive Disruption During Studies of Hypoglycaemia</b>	<b>References</b>
<i>Many aspects of brain function become impaired at blood glucose concentrations below 3.0 mmol/l</i>	Holmes et al, 1983, 1984, 1986, Pramming et al, 1986, Heller et al, 1987, Hoffman et al, 1989, Stevens et al, 1989, Blackman et al, 1990, Widom and Simonson, 1990, Kerr et al, 1991b, Mitrakou et al, 1991
<i>Simple motor functions are resistant to the effects of hypoglycaemia</i>	Holmes et al, 1983, Herold et al, 1985, Holmes et al, 1986, Pramming et al, 1986, Stevens et al, 1989, Hoffman et al, 1989, Wirsén et al, 1992, Cox et al, 1993b
<i>There is considerable inter-individual variation in test results</i>	Herold et al, 1985, Hoffman et al, 1989, Widom and Simonson, 1990, Cox et al, 1993b, Draelos et al, 1995
<i>Disrupts the speed of information processing</i>	Tallroth et al, 1990, Jones et al, 1990
<i>Accuracy is often preserved at the expense of speed</i>	Holmes et al, 1983, Heller et al, 1987
<i>Tests which involve speeded responses and which are more cognitively complex and attention demanding become impaired</i>	Widom and Simonson, 1990
<i>It takes 40 to 90 minutes after the blood glucose returns to normal for brain function to return to normal</i>	Blackman et al, 1992, Lindgren et al, 1996

### **2.1.3 Limitations of cognitive function testing in studies of hypoglycaemia**

Various authors have reviewed the main effects of acute hypoglycaemia on cognitive performance [Deary, 1993b, Deary, 1999, Heller & Macdonald, 1996]. They have alluded to the problems of experimental design inherent in many of these studies. In the earlier experiments, different methods of induction of hypoglycaemia were used, with some investigators using an insulin infusion [Russell & Rix-Trot, 1975], and others using a hyperinsulinaemic glucose clamp [Holmes et al, 1983]. This meant that subjects in the infusion studies were exposed to a rapid change in blood glucose and insulin concentrations, both representing confounding variables that may have impacted on neuropsychological testing. By contrast, the clamp studies apply a constant rate of insulin infusion achieving high concentrations of insulin and are now the methodology of choice in such studies. It is pertinent to note that although the higher rates of insulin infusion have been shown to attenuate the symptomatic and neuroendocrine responses to hypoglycaemia, they do not appear to influence the cognitive response to comparable levels of hypoglycaemia (Kerr et al, 1991a, Fanelli et al, 1994).

One other problem with the earlier studies of hypoglycaemia was that different methods of blood sampling were used, with some investigators reporting plasma whereas others used whole blood glucose values. This is important for comparison because plasma produces a glucose value around 10-20% higher than the equivalent whole blood glucose concentration [Foster et al, 1978]. Furthermore, in studies of cognitive function, it is important to assess the arterial blood glucose concentration, so it is now accepted practice to incorporate sampling from a hand vein which has been warmed, either in a heated blanket or box, to closely approximate arterialised blood [McGuire et al, 1976]. However, many previous studies have used standard venous samples drawn from the antecubital fossa [Heller & Macdonald, 1996].



Concerns have also been raised regarding the different ability levels of subjects used in studies of cognitive function [Deary, 1999] with the suggestion that subjects with a higher intelligence may be more susceptible to the effects of neuroglycopenia [Gold et al, 1995a]. Furthermore, other factors may affect the cognitive response to hypoglycaemia such as age and sex and glycaemic exposure (see later). Therefore, studies may report different results simply because different subjects were examined.

In addition, it is often difficult to precisely identify the cognitive processes that are being measured with neuropsychological testing, and the heterogeneity of many of the test batteries employed make it difficult to extrapolate the results to everyday tasks. Because of this, a lack of consensus remains as to the appropriate tests for measurement of cognitive function [Strachan et al, 1997, Amiel, 1998]. There remains a wide selection of tests to measure speed of information processing, but there is considerable overlap with other cognitive processes such as reaction time, visual sensory processing and motor coordination. Because many of the commonly used tests of cognitive function in hypoglycaemia are timed, and the major effect of hypoglycaemia during these tests is on speed rather than ability, the effects of hypoglycaemia may be overstated. Finally, because many studies have been underpowered, negative results may have been due to type 2 statistical errors, adding a further difficulty when trying to compare studies.

The following section will examine the evidence for deterioration of attentional abilities, intelligence and motivation, which form the basis of this thesis, during controlled insulin-induced hypoglycaemia.



## 2.2 SPECIFIC COGNITIVE DOMAINS

### 2.2.1 Attention

Many investigators have used their results from experimental glucose clamp studies to assert that attentional abilities in adults with type 1 diabetes [Holmes et al, 1983, 1984, Harrad et al, 1985, Pramming et al, 1986, Hoffman et al, 1989, Widom & Simonson, 1990] and in healthy volunteers [Harrad et al, 1985, Ipp and Forster, 1987, Stevens et al, 1989, Mitrakou et al, 1991, McCrimmon et al, 1996, McCrimmon et al, 1999a, Strachan et al, 2001] are sensitive to hypoglycaemia. However, although these studies claim to examine attention, many have used a range of neuropsychological tests that involve attention. Therefore, a fundamental problem with the examination of attention is that all tests are 'contaminated' to some extent by attentional processes. Hence, because attention is a fundamental cognitive process that is integral to many neuropsychological tests, the isolated identification of attentional dysfunction is a difficult undertaking.

In the study of 12 volunteers with type 1 diabetes by Holmes et al [1983], the Matching Familiar Figures Test (MFFT) and delayed reaction time were used to index attentional abilities. The attention to, and the performance on a reaction time task, was slowed during hypoglycaemia. By contrast, there was no effect of hypoglycaemia on the MFFT [Holmes et al, 1983]. Deterioration in simple reaction time has been detected in non-diabetic subjects at blood glucose concentrations of 2.0, 2.4 and 2.7 mmol/l [Herold et al, 1985, Mitrakou et al, 1991, Wirsén et al, 1992]. However, to effect this change, the degree of hypoglycaemia has to be quite severe because Stevens and colleagues showed no effect on a simple reaction time test at a blood glucose concentration of 3.4 mmol/l [Stevens et al, 1989].

In a later study by Holmes and her colleagues [1984], the Stroop test [Trener et al, 1989], which measures several cognitive processes including selective attention, was administered to 12 young male subjects, aged 18 to 35 years, with

type 1 diabetes. In that study, the Stroop task of naming dot colours and ink colours was significantly slowed at a blood glucose concentration of 3.3 mmol/l. In the study of 10 non-diabetic volunteers by Mitrakou et al [1991], the Stroop test was impaired at an arterialised blood glucose concentration of 2.4 mmol/l, but not at 3.1 or 3.7 mmol/l.

Hoffman et al [1989] administered a variety of cognitive tests to 18 subjects with type 1 diabetes at blood glucose concentrations of 2.7, 5.6 and 16.6 mmol/l. The Trail making B (TMB) test, in which subjects connect numbered and labelled points in sequence, measures selective attention and divided attention in addition to working memory, deteriorated significantly during hypoglycaemia. This finding with the Trail making B test has been replicated by other investigators during hypoglycaemia in non-diabetic volunteers [Stevens et al, 1989, Widom and Simonson, 1990, Mitrakou et al, 1991, McCrimmon et al, 1996, McCrimmon et al, 1999a, Strachan et al, 2001] and in subjects with type 1 diabetes [Pramming et al, 1986, Widom & Simonson, 1990]. In the study by Ipp and Forster [1987], although TMB failed to deteriorate in seven non-diabetics at a blood glucose concentration of 3.6 mmol/l, it was markedly affected at a plasma glucose concentration of 2.1 mmol/l in a substudy of four volunteers ( $p < 0.01$ ).

Harrad et al [1985] administered the Farnsworth test, a measure of sustained attention and concentration over a long period, to six control subjects and five subjects with type 1 diabetes at blood glucose concentrations of 2.5 and 1.5 mmol/l and at blood glucose concentrations greater than 4.0 mmol/l. In that study, the Farnsworth test deteriorated significantly during hypoglycaemia. In a large study of 42 subjects with type 1 diabetes, Draelos et al employed the digit vigilance test as a measure of sustained attention and reported this to be profoundly affected by hypoglycaemia [Draelos et al, 1995]. In this test, subjects are given a page containing rows of digits and instructed to cancel target digits (either the number 6 or 9). The number of targets located in 2

minutes as well as the percentage of targets erroneously missed are scored, providing measures of speed and accuracy. However, it is highly likely that this test is measuring speeded processing, and this may account for the significant deterioration in this subtest in the study by Draelos et al [1995]. Digit vigilance has also been included in the test batteries used by others [Mitrakou et al, 1991, Mokan et al, 1994, Fanelli et al, 1993, 1994, Veneman & Van Haeften, 1994] where overall z scores have deteriorated at plasma glucose concentrations ranging between 2.4 and 3.0 mmol/l.

Therefore, there is a considerable weight of evidence to back the assertion that attention-demanding tasks are impaired during moderate insulin-induced hypoglycaemia.

### **2.2.2 Fluid intelligence**

Very few studies of acute hypoglycaemia have included subtests specifically designed to measure aspects of intelligence. One of the first studies to attempt an examination of this modality administered simple arithmetic problems to twelve people with type 1 diabetes [Holmes et al, 1983]. This demonstrated that fewer mathematical computations were correctly completed at a blood glucose level of 3.3 mmol/l compared to normal and high blood glucose concentrations. However, Holmes and her colleagues noted in their discussion that the percentage of correct math problems to the number of problems attempted showed no treatment or glucose effects, suggesting that the subjects had preserved accuracy at the expense of speed during the tests as discussed earlier.

The Digit Symbol Task (DSST), a subtest of the Performance IQ scale of the Wechsler battery of intelligence tests [Wechsler & Stone, 1981] was included in a battery of tests administered to 12 non-diabetic volunteers [Stevens et al, 1989]. In that study, the DSST showed significant impairment at an arterialised blood glucose concentration of 3.4 mmol/l. In a further study of 20 non-diabetic volunteers, the DSST was disrupted at arterialised blood glucose levels of 2.5

mmol/l [McCrimmon et al, 1996]. Similar findings were reported in the study of 16 non-diabetic subjects by Strachan et al [2001] during moderate hypoglycaemia (2.6 mmol/l), and in 20 healthy volunteers exposed to an arterialised blood glucose concentration of 2.5 mmol/l [Gold et al, 1995a].

Kerr and colleagues [1991b] examined a range of cognitive processes in nine subjects with type 1 diabetes. There was a significant decline in scores for the DSST at a mean arterialised blood glucose of 2.8 mmol/l. Similar findings were described in a further two studies of subjects with type 1 diabetes at blood glucose concentrations of 1.98 [Wirsén et al, 1992] and 2.5 mmol/l [Gold et al, 1995a].

### **2.2.3 Motivation and workload**

The tests of cognitive function utilised during studies of hypoglycaemia have been criticised as being imperfect because of the perceived practice effect that may take place, i.e. repetition of the test will improve performance [Heller & Macdonald, 1996]. The resulting improvement results from practice and will diminish the impairment caused by hypoglycaemia, leading to the incorrect conclusion that cognitive function is unaffected or only modestly impaired. Furthermore, fatigue may increase the sensitivity of cognitive tests, in that those tests attempted at the end of a test period may be more sensitive to the effects of hypoglycaemia [Heller & Macdonald, 1996]. It may also be difficult to discriminate the effects of affect, or mood, from those of its cognitive and motivational concomitants. For example, the effects of anxiety on behaviour might be mediated by affect (e.g. tension) or by cognitions (e.g. intrusive thoughts and worries), or by motivations, such as the urge to withdraw from the threatening situation. Another variable is that the motivation to perform a task may decline over the cognitive function testing period and between test days, thereby influencing the results. Effort reduction is a common response to tasks that have little perceived value [Hockey, 1997]. Therefore, it is surprising that



no studies have examined the role of motivation and workload on the cognitive responses to hypoglycaemia.

## **2.3 EMOTIONS**

### **2.3.1 Mood**

In view of the unpleasant symptoms that are generated by hypoglycaemia, it is surprising that the effects of acute hypoglycaemia on emotions did not receive a rigorous research effort until the 1990s. However, early reports did suggest a deleterious effect of hypoglycaemia on behaviour and personality [Fischer & Dolger, 1946, Jones, 1947], and in a more recent study by Gonder-Frederick et al [1989], low blood glucose concentrations were associated with negative mood states such as nervousness.

In the study by Hepburn and colleagues, an insulin infusion was used to induce hypoglycaemia in 12 non-diabetic subjects and 15 subjects with type 1 diabetes [Hepburn et al, 1995]. A significant increase in tense arousal and a decline in energetic arousal occurred during hypoglycaemia. In other words, hypoglycaemia provoked a state of increased anxiety and lethargy. However, a significant limitation of this study was the lack of a control arm, so it is possible that the stress and fatigue associated with the tests per se may have led to the observed changes in mood.

In two subsequent studies, a hyperinsulinaemic glucose clamp technique was used to induce controlled hypoglycaemia, and a euglycaemic control limb was incorporated [Gold et al, 1995c, McCrimmon et al, 1999a]. In one study, a hyperinsulinaemic glucose clamp was used to induce hypoglycaemia in 24 non-diabetic adults [Gold et al, 1995c]. Hypoglycaemia induced significant increments in the scores for tense arousal with a simultaneous decrement in the score for energetic arousal [Gold et al, 1995c]. In a further report of healthy adult volunteers McCrimmon and colleagues used an identical study design to demonstrate a rise in anxiety levels during hypoglycaemia. Furthermore, in both

these studies of non-diabetic subjects, subjects became less happy (hedonic tone) during hypoglycaemia [Gold et al, 1995c, McCrimmon et al, 1999a]. In a subsequent study, McCrimmon and colleagues demonstrated an increase in anger scores during controlled hypoglycaemia, a finding that is compatible with the symptom of aggression, or even frustration, that is occasionally manifest as an expression of hypoglycaemia in some individuals [McCrimmon et al, 1999b].

## 2.4 INFLUENCES ON COGNITIVE FUNCTION DURING ACUTE HYPOGLYCAEMIA

At the beginning of this chapter the substantial inter-individual differences in mental disruption during hypoglycaemia were highlighted. A number of factors are associated with susceptibility to cognitive disruption during hypoglycaemia including age, gender, IQ, the diagnosis of diabetes per se, with the effects of glycaemic control and antecedent hypoglycaemia, and a history of impaired awareness of hypoglycaemia (table 2.2).

**Table 2.2** Potential influences of cognitive disruption during hypoglycaemia

<b>Potential Moderator</b>
Age
Gender
IQ
Diagnosis of diabetes
Glycaemic control
Antecedent hypoglycaemia
Impaired awareness of hypoglycaemia

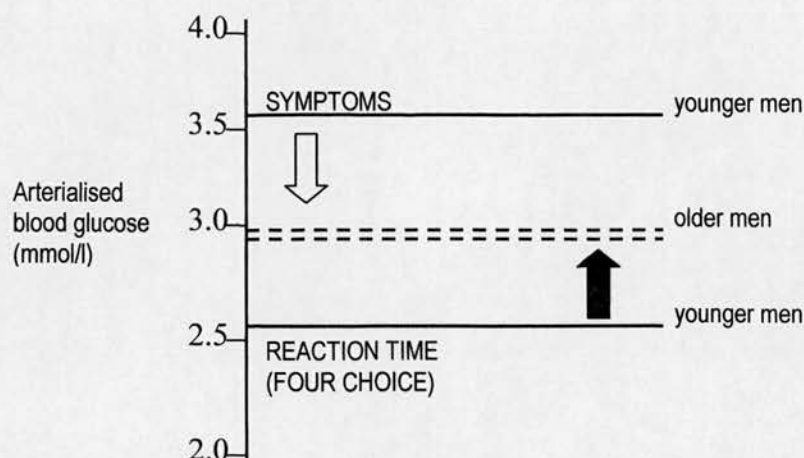


### **2.4.1 Age**

The hierarchy of the cognitive changes in response to hypoglycaemia may change with age. In the study of non-diabetic subjects by Matyka et al [1997] the responses to moderate hypoglycaemia of seven elderly men were compared with those of seven young men. The four-choice reaction time, a measure of psychomotor coordination, deteriorated in the older men at a mean (SD) plasma glucose of 3.0 (0.1) mmol/l compared to 2.6 (0.1) mmol/l in the young group, and the abnormality was more profound (figure 2.1). Because the symptomatic response to hypoglycaemia commenced at a lower blood glucose concentration in the older men than in the young adults (3.0 (0.2) vs. 3.6 (0.1) mmol/l), in the older subjects the glycaemic threshold for subjective symptomatic awareness of hypoglycaemia and that for the onset of cognitive dysfunction was coincidental. A similar problem has been observed in patients with type 1 diabetes who have developed impaired awareness of hypoglycaemia, in whom the onset of the cognitive dysfunction induced by hypoglycaemia either preceded or was coincidental with the onset of a symptomatic response [Frier & Fisher, 1999]. This observation suggests that the elderly may be at an intrinsically greater risk of developing neuroglycopenia because the onset of warning symptoms and cognitive impairment occur simultaneously, so interfering with their ability to recognise and take action to self-treat a low blood glucose.

### **2.4.2 Gender**

In a study by Draelos et al [1995] of 20 men and 22 women with type 1 diabetes, aged 18 to 44 years, significant gender differences on two cognitive tests during hypoglycaemia were reported. At a mean blood glucose concentration of 2.2 mmol/l, women performed better than men on the trail making test ( $p=0.02$ ) and on the percentage of errors component of the digit vigilance test ( $p=0.03$ ). Interestingly, these tests also measure selective and sustained attention as well as mental flexibility. No other significant gender cognitive differences were noted.



**Figure 2.1** The difference between the glycaemic threshold for subjective awareness of hypoglycaemia and that for the onset of cognitive dysfunction may be absent in the elderly. Reproduced from *Diabetes in Old Age* 2<sup>nd</sup> edition, 2001 (eds AJ Sinclair and P Finucane). Copyright 2001, John Wiley & Sons Limited, reproduced with permission

### 2.4.3 Intelligence Quotient

It has been suggested that people with very high IQs may have a greater disruption to mental function during hypoglycaemia than people with average IQs. This was based on the mooted assertion that a higher intelligence might offer protection against cerebral insult because of increased ‘brain reserve capacity’ during brain processing [Maylor et al, 1990, Saltz, 1993].

In a study of 24 non-diabetic subjects, Gold et al [1995a] lowered the arterialised blood glucose from 4.5 mmol/l to 2.5 mmol/l. The subjects were divided into a high IQ group (equivalent to top 30% of University students) and average IQ group (bottom 12% of University students) on the basis of the National Adult Reading Test (NART) and Alice 4 Heim tests. In a univariate analysis, the average IQ group deteriorated significantly less than the higher IQ group during hypoglycaemia in only one of 4 tasks administered ( $p=0.03$ ), and

may have been a type 1 statistical error. This was supported by the study of Draelos and colleagues, where a higher IQ did not affect the cognitive disruption during hypoglycaemia [Draelos et al, 1995].

#### **2.4.4 Diagnosis of diabetes**

Some investigators have suggested that a diagnosis of diabetes confers susceptibility to cognitive dysfunction during hypoglycaemia [Wirsén et al, 1992]. In that study a battery of neuropsychological tests were administered to ten male subjects with type 1 diabetes (median age 25 years) and 12 non-diabetic volunteers (median age 25 years). Blood glucose concentrations were lowered to approximately 2.0 mmol/l in both groups. The investigators found that the diabetic subjects performed less well in areas such as perceptual speed and reaction times [Wirsén et al, 1992]. However, the subjects with diabetes started at a higher blood glucose concentration (5.85 vs 4.56 mmol/l) and so had a proportionately greater fall in blood glucose, which may have affected the results. Furthermore, both groups were from different occupational backgrounds (the diabetics were white collar workers and the non-diabetic subjects were medical students), and there was poor matching of pre-morbid cognitive ability [Deary, 1993b]. In two other studies, no significant differences in cognitive dysfunction were noted between groups of diabetic and non-diabetic subjects [Herold et al, 1985, Widom & Simonson, 1990]. Finally, although Heller and colleagues demonstrated reaction time testing to be significantly faster in non-diabetic volunteers compared to diabetic subjects, the non-diabetic subjects were younger and more intelligent, two important variables known to affect reaction time [Heller et al, 1987]. Therefore, the issue of whether diabetes is a factor that moderates an individual's susceptibility to cognitive dysfunction during hypoglycaemia remains unresolved.

#### **2.4.5 Glycaemic control, antecedent hypoglycaemia and impaired awareness**

##### *Glycaemic control*

Due to the dynamic response of the glycaemic thresholds for the neurohumoral and symptomatic response to changes in glycaemic control, it is not unreasonable to propose that similar changes may occur with cognitive disruption. However, there is considerable interaction between these three areas, making it difficult to study them in isolation. Nonetheless, in the study by Amiel and colleagues, subjects with good glycaemic control developed electroencephalographic (EEG) changes at higher blood glucose levels than subjects with poor glycaemic control, suggesting a dissociation between neuroglycopenic symptoms and cognitive disruption [Amiel et al, 1991].

In a study by Widom and Simonson [1990], eight subjects with good glycaemic control (HbA1 8.0% (0.2%)) were compared with nine subjects with poor glycaemic control (HbA1 11.8% (0.4%)), and ten non-diabetic volunteers. A hyperinsulinaemic glucose clamp was used to lower the plasma glucose from 5.0 mmol/l to 2.2 mmol/l. Although an increase in the glycaemic threshold for the symptomatic and neuroendocrine response to hypoglycaemia was observed, there was no difference in the median glucose threshold for cognitive dysfunction in any of the tests administered.

Maran and colleagues examined subjects with well-controlled diabetes who reported the onset of autonomic and neuroglycopenic symptoms at blood glucose concentrations of 2.4 and 2.3 mmol/l, whereas subjects with less strict glycaemic control and non-diabetic individuals' responses began at significantly higher levels, between 2.8 and 3.0 mmol/l. However, for all three groups, the reaction time test deteriorated at blood glucose concentrations between 2.8 and 3.0 mmol/l, thus seriously disadvantaging the intensively treated group who had the onset of cognitive deterioration before the warning symptoms of hypoglycaemia [Maran et al, 1995]. However, in another study by Zeigler and colleagues, seven diabetic subjects with strict glycaemic control (mean HbA1c

6.3%) were compared with 11 with less good control (HbA1c 9.1%). In that study, an intravenous insulin infusion was used to lower the blood glucose concentration over a 50 minute period. The threshold for the P300 wave occurred at a lower blood glucose concentration than the latter (1.6 mmol/l vs 3.5 mmol/l,  $p < 0.05$ ) [Zeigler et al, 1992], contrary to the findings of Amiel et al [1991]. Equivalent results were found in the study by Jones et al [1997].

#### *Antecedent hypoglycaemia*

We know that the reduced adrenaline response to hypoglycaemia following a recent episode of hypoglycaemia lasts about 6 days (see section 1.6.5) and is specific to that stimulus. However, does a history of antecedent hypoglycaemia affect the cognitive response to subsequent hypoglycaemia? The available published studies give conflicting results. Whereas Mellman et al [1994] found that scores on the Logical Memory test in non-diabetic subjects during hypoglycaemia were attenuated by a prior two hour period of antecedent hypoglycaemia, Hvidberg and colleagues [1996] found no effect of antecedent hypoglycaemia (arterialised plasma glucose of 2.6 mmol/l for two hours) on overall cognitive performance during a stepped hypoglycaemic clamp. Freuhwald-Schultes and colleagues examined cognitive function during a stepped hypoglycaemic clamp at 4.1, 3.6, 3.1 and 2.6 mmol/l in 30 non-diabetic volunteers over a 6 hour period [Freuhwald-Schultes et al, 2000]. 15 of the volunteers received an additional 150 minute antecedent hypoglycaemic clamp on the preceding day. In that study, following antecedent hypoglycaemia, there was attenuation not only of the amplitude of the P3 of the auditory-evoked brain potential, but also in a test of short term memory and reaction time.

The findings in three studies of subjects with type 1 diabetes are also conflicting. In the study of 15 subjects with type 1 diabetes, Dagago-Jack [1993] found that scores for attention were actually worse during moderate hypoglycaemia following a period of antecedent hypoglycaemia the day before. In a further study of eight diabetic subjects, George et al [1995] confirmed no



effect of antecedent hypoglycaemia on the glycaemic threshold for impairment of four-choice reaction time during hypoglycaemia, despite a blunted catecholamine response. Ovalle et al [1998] induced twice weekly hypoglycaemia (plasma glucose of 2.8 mmol/l for two hours) in six diabetic subjects for one month. In a subsequent stepped hypoglycaemic clamp, there was less deterioration in cognitive function despite an expected blunting of the symptomatic and neurohumoral responses to antecedent hypoglycaemia.

Most insulin regimens cause nocturnal hyperinsulinaemia and predispose to nocturnal hypoglycaemia which occurs in up to 50% of people treated with insulin, is asymptomatic in 25-75% of episodes and may last for up to six hours [Tattersall, 1999]. Two studies have examined the cognitive effects of antecedent nocturnal hypoglycaemia [Veneman et al, 1993, Fanelli et al, 1998]. In the first study of 10 non-diabetic subjects, a lowering of the plasma glucose to 2.4 mmol/l for two hours on the day prior to study, lessened the degree of cognitive disruption during subsequent hypoglycaemia the following day. In a study of 15 subjects with type 1 diabetes, Fanelli and colleagues found that antecedent hypoglycaemia of 2.8 mmol/l for 3.5 hours reduced overall cognitive function during subsequent hypoglycaemia the following day [Fanelli et al, 1998].

This important topic would not be complete without reference to the extraordinary experiment by Boyle and colleagues where brain glucose uptake (BGU), the neuroendocrine response and cognition were examined in 12 non-diabetic humans during two stepped glucose clamps, at glucose concentrations of 4.2, 3.6, 3.1 and 2.5 mmol/l [Boyle et al, 1994]. Between the two clamps, the blood glucose was maintained at 2.9 mmol/l. Although BGU was impaired at a blood glucose concentration of 3.6 mmol/l on the first clamp, it was not impaired at any level after 56 hours of hypoglycaemia. As expected, the onset of the neuroendocrine and symptomatic response occurred at lower levels of blood glucose in the second clamp. However, decrements in two out of four



cognitive tests were delayed following 54 hours of hypoglycaemia [Boyle et al, 1994]. Although these results suggest a comprehensive cerebral response to antecedent fuel supply, this alteration in cognitive threshold did not occur after a shorter period of sustained hypoglycaemia [Gold et al, 1995d]. Furthermore, there was no control for practice effects and there were no statistical interaction analyses between clamps, thus making it easier to find a sham effect in line with the experimental hypothesis.

#### *Impaired awareness of hypoglycaemia*

Few studies have evaluated how a diagnosis of impaired awareness of hypoglycaemia impacts on cognitive disruption during hypoglycaemia. Furthermore, the study of this important area is hindered by a lack of consensus definition of impaired awareness of hypoglycaemia, by the aforementioned considerable interrelation with strict glycaemic control and antecedent hypoglycaemia, and by the lack of a consensus agreement on a validated battery of cognitive tests for use in hypoglycaemia.

In the study by Gold et al [1995b], a self-rating scale was used to measure impaired awareness in which subjects scored how often they had symptoms during spontaneous hypoglycaemia. In that study, the subjects with impaired awareness appeared to show more profound cognitive disruption during acute hypoglycaemia, which persisted for longer following blood glucose recovery. By contrast, in an earlier study of 11 subjects type 1 diabetes with impaired awareness of hypoglycaemia and four with normal awareness, there was no difference in cognitive performance as assessed by four-choice reaction time [Heller et al, 1987].

An alternative mode of examining this process is by testing cognitive function following restoration of awareness of hypoglycaemia, by avoidance of hypoglycaemia. In the study by Fanelli et al [1993], this was associated with a rise in the blood glucose threshold for cognitive dysfunction from 2.5 to 3.0

mmol/l. However, in another study of 12 subjects with type 1 diabetes, half with good control and half with poor control, hypoglycaemia was avoided for a period of three weeks. Although the glycaemic thresholds for hormonal and symptomatic responses to hypoglycaemia were raised during a stepped hypoglycaemic clamp, the threshold for cognitive disruption remained unchanged at 2.8 mmol/l [Cranston et al, 1994].

#### **2.4.6 Adaptation to hypoglycaemia**

Patients who have impaired awareness of hypoglycaemia frequently record biochemical hypoglycaemia, which is asymptomatic, suggesting the development of an adaptation to neuroglycopenia. Therefore, the impact of the duration of hypoglycaemia on cognitive function has been examined in a number of studies. In the study of 24 non-diabetic subjects by Gold et al [1995d], short term exposure (40-60 minutes) to moderate hypoglycaemia (2.5 mmol/l) led to no improvement in cognitive function and no reduction in symptom scores. By contrast, two earlier studies in subjects with [Kerr et al, 1991b] and without diabetes [Kerr et al, 1989], showed an improvement in tests of cognitive function after a period of 60-90 minutes. However, in these two studies, no direct statistical comparisons were made between euglycaemia and hypoglycaemia, and there was evidence of a practice effect on the reaction time task used, whereas the Edinburgh study controlled for both of these variables [Gold et al, 1995d]. In a more recent study, cognitive function was assessed (using four-choice reaction time, Stroop word and colour-word test) repeatedly using a hyperinsulinaemic glucose clamp in eight non-diabetic volunteers. During moderate hypoglycaemia (arterialised plasma glucose of 2.6 mmol/l) for 90 minutes, there was no attenuation of the hormonal, symptomatic or cognitive responses during sustained hypoglycaemia [Evans et al, 2000], thus supporting the earlier results found by Gold and colleagues [Gold et al, 1995d].

The possibility that a longer duration of hypoglycaemia would lead to cerebral adaptation was suggested in the study by Bendtson and colleagues, where no

cognitive impairment was identified after severe nocturnal hypoglycaemia [Bendtson et al, 1992]. In the experiment by Boyle and colleagues of non-diabetic volunteers who were subjected to a prolonged period of hypoglycaemia for 56 hours, BGU was prolonged after chronic hypoglycaemia, and the glycaemic thresholds for the neuroendocrine, symptomatic and cognitive responses to hypoglycaemia were increased, suggesting an effect of cerebral adaptation during chronic neuroglycopenia [Boyle et al, 1994]. However, in that study the degree of hyperinsulinaemia was uncontrolled and may have had a direct effect on cerebral function [Kerr et al, 1991a].

## **2.5 Summary and clinical importance of cognitive disruption during hypoglycaemia**

Acute hypoglycaemia, of the depth and duration often experienced by patients with type 1 diabetes, causes cognitive dysfunction. This develops at around 3.0 mmol/l and affects many aspects of cognition including attention-demanding tasks, mental flexibility, psychomotor skill and long-term memory. Non-cognitive disruption during hypoglycaemia promotes an expression of negative mood states including diminished energetic arousal, decreased happiness, increased anxiety and increased anger. A hierarchy exists in the sensitivity of different aspects of cognition, with complex tasks being more severely impaired than simpler cognitive tasks. Accuracy of tasks is often preserved at the expense of speed.

Although a pronounced inter-subject variability is apparent for the blood glucose thresholds at which impairment of particular cognitive tasks commence, the precise moderators of cognitive dysfunction remain unclear. While older people and men may be more susceptible to cognitive disruption during hypoglycaemia, the available evidence suggests that current intelligence and the diagnosis of diabetes per se do not moderate the response. The complex interrelation of glycaemic control, antecedent hypoglycaemia and impaired awareness is a highly contentious area and remains unresolved. Whereas some

commentators hold the view that cognitive dysfunction is not affected by antecedent hypoglycaemia, an increasing number of studies suggest that the glycaemic threshold is indeed raised, similar to the neuroendocrine and autonomic symptom response [Veneman et al, 1993, Ovalle et al, 1998, Fanelli et al, 1998, Freuhwald-Schultes, 2000]. Much of the controversy is related to methodical differences between studies pertaining to the heterogeneity of the subjects, sample sizes and the neuropsychological tests used.

Short-term cerebral adaptation to hypoglycaemia does not occur but is a maladaptive response to more prolonged hypoglycaemia, predisposing the individual to severe hypoglycaemia. During prolonged hypoglycaemia, brain glucose uptake is promoted through the upregulation of GLUT1 and GLUT3 molecules [Kumagai et al, 1995]. This enhanced central glucose uptake during hypoglycaemia may prevent neuroglycopenia, thereby reducing cognitive dysfunction during hypoglycaemia. Alternatively, the weakened neuroendocrine response after antecedent hypoglycaemia, through the effects of cortisol release, may contribute to the attenuation of cognitive disruption.

#### *Importance and validity of cognitive dysfunction during hypoglycaemia*

Are the cognitive changes during acute hypoglycaemia of consequence and valid? It is widely recognised that there is a need to study the effects of hypoglycaemia on brain function so that clinical practice may be better informed. Although various general psychometric tests and tests of reaction time have confirmed the existence of cognitive dysfunction during acute hypoglycaemia, in terms of specificity, they are analogous to the erythrocyte sedimentation rate used in general medicine. Further research is required to elucidate the specific psychological processes affected by hypoglycaemia. Understanding these processes provides information that will be useful to diabetes educators and policy makers. Moreover, further research needs to demonstrate that impairments in laboratory cognitive tasks have a bearing on mental performance in important practical and work-related abilities.



Driving simulator studies have demonstrated impairment of driving skills during moderate hypoglycaemia (2.6 mmol/l) [Cox et al, 1993c] and mild hypoglycaemia (3.4-4.0 mmol/l) [Cox et al, 2000]. In the earlier study by Cox et al [1993c], during hypoglycaemia, more than one third of individuals with type 1 diabetes demonstrated more spinning, swerving, time off the midline and the road. In keeping with earlier observations about accuracy preservation at the expense of speed, there was more very slow driving. In the later study, it was worrying that subjects were generally unaware of their poor driving skills and that the mean glucose level at which they took corrective action was 2.7 mmol/l [Cox et al, 2000]. Although these studies are useful, they have been criticised for not being relevant to real driving experience.

An alternative strategy to assess the importance of cognitive dysfunction during hypoglycaemia is the investigation of the more basic brain processes and human information processing. A preliminary examination of language function was carried out by Holmes and colleagues who demonstrated impairment of verbal fluency [Holmes et al, 1984]. More recent studies have shown that although acute hypoglycaemia has no effect on visual acuity or stereoscopic vision in non-diabetic subjects [McCrimmon et al, 1996], it does disrupt visual information processing using measures of visual inspection time, simple visual discrimination and the speed of transfer of visual information to decision-making processes [Ewing et al, 1998]. In a further study of 15 adults with type 1 diabetes, the same investigators found that moderate hypoglycaemia (arterialised blood glucose of 2.6 mmol/l) caused deterioration in single tone loudness and in auditory temporal processing [Strachan et al, 2003].

In Chapters 6 and 7 of this thesis the results of original research will be presented that used a batch of tests specifically designed to assess attentional processes and intelligence. In Chapter 8, new data will be reported on tests of workload and subjective cognition both of which are two important areas that have not been studied previously in hypoglycaemia.

**CHAPTER 3**

**ATTENTION, MOTIVATION AND INTELLIGENCE**



### **3.1.1 The concept of attention**

The concept that attention is central to human performance has been recognised in experimental psychology for more than a century [James, 1890]. However, it was not until relatively recently that developments in neuroscience revealed a system of anatomical areas that appear to be basic to the selection of information for focal, or conscious, processing [Wurtz et al, 1980, Raichle, 1983]. Although knowledge of the precise neural mechanisms responsible for these operations is still incomplete, many of the brain areas and networks involved have been identified. Furthermore, there is evidence that damage to some of these networks produces similar symptoms regardless of whether the cause is cerebrovascular disease, psychopathology or developmental [Posner & Cohen, 1994]. Therefore, it is now recognised that attention is a complex mental ability involving multiple subcomponent processes [Posner and Peterson, 1990], and several independent attention systems in the brain serve different functions.

Although all neurons are selective in the range of activation to which they will respond, the role of the attention system is to modulate this selection for those types of stimuli that might be most important at a given moment. Three fundamental findings can be attributable to attention. Firstly, the attention system of the brain is anatomically separate from the data processing systems that perform operations on specific inputs even when attention is directed elsewhere. Therefore, although the attention system interacts with other parts of the brain, it maintains its own individuality. Secondly, attention is not the property of a single centre in the brain, nor a general function of the brain in its entirety, i.e. attention is carried out by a network of anatomical areas [Mesulam, 1981, Rizzolatti et al, 1985]. Finally, the areas involved in attention carry out different functions [Posner et al, 1988].

The attentional processes that have been studied most frequently involve focusing, selecting, dividing, sustaining, suppressing, and inhibiting attention. Although no dominant theory can integrate all of these components within a

unifying framework, several models have been proposed that support the concept of fractionation of attention into different supramodal systems each of which has a distinct neuroanatomical basis [Posner & Peterson, 1990]. Using the concept that attention is fractionated into different supramodal systems, it has been proposed that attention consists of at least three separate systems [Posner & Peterson, 1990]. A selection system is responsible for selecting relevant stimuli/processes and inhibiting irrelevant ones, a vigilance system maintains readiness to respond in the absence of external cues and an orientation system is responsible for engaging, moving and disengaging attention in space.

### **3.1.2 Attentional systems**

#### *Orientation system*

The sensory responses of neurons in several areas of the brain have been shown to discharge at a greater rate when the orientation system is engaged. For example, when a monkey is directed to a specific location, as opposed to some other random spatial location, three areas of enhancement occur within the brain; the posterior parietal lobe [Mountcastle, 1978, Wurtz et al, 1980], the lateral pulvinar nucleus of the postereolateral thalamus [Petersen et al, 1987], and the superior colliculus. Similar effects in the parietal cortex have been shown in normal humans using positron emission topography [Petersen et al, 1988a]. Likewise, when people are asked to move their eyes towards a specific target, an improvement in efficiency at the target location occurs well before the eyes move [Remington, 1980], and it is thought that this covert shift of attention functions as a way of guiding the eye to an appropriate area within the visual field [Fischer & Breitmeyer, 1987, Posner & Cohen, 1984].

As you might expect, brain injury to any of the mentioned three areas in humans causes a reduction in the ability to shift attention covertly [Posner, 1988], although the deficit produced varies between areas. For example, damage to the posterior parietal lobe has its greatest effect on the ability to disengage from an

attentional focus [Posner & Cohen, 1984], whereas a lesion of the superior colliculus results in an inability to shift attention.

### *Selection system*

Studies of attention have shown that detecting a target produces widespread interference with most other cognitive processes [Posner, 1978]. However, monitoring many spatial locations or modalities produces little or no interference over monitoring a single modality, unless a target occurs [Duncan, 1980]. This finding supports the distinction between a general alert state and one in which attention is clearly orientated and engaged in processing information. Petersen et al [1988b] have shown that the anterior cingulate gyrus and the supplementary motor area are active during the processing of words. Further evidence to support the concept that the anterior cingulate is involved in target detection comes from Posner et al [1988] who demonstrated that the degree of blood flow in the anterior cingulate increases as the number of targets to be detected increases.

### *Vigilance system*

An important attentional function is the ability to prepare and sustain alertness to process high priority signals. Anatomical evidence has accumulated on the nature of the systems producing a change in the alert state. A consistent finding is that the ability to develop and maintain the alert state depends heavily upon the integrity of the right cerebral hemisphere [Heilman et al, 1985]. This fits very well with the observation that patients with right hemispheric lesions show signs of neglect, and that performance in vigilance tasks is more impaired with right rather than left lesions [Coslett et al, 1987, Wilkins et al, 1987]. Furthermore, it has been noted in split-brain patients that vigilance is poor when information is presented to the isolated left hemisphere, but is relatively good when presented to the isolated right hemisphere [Diamond & Beaumont, 1973]. In addition, cerebral blood flow and metabolic studies also argue for a link

between the right cerebral hemisphere and the vigilance system [Cohen et al, 1988, Deutsch et al, 1987].

Neuropathological observations have indicated that the brain is susceptible to neuroglycopenia in a rostrocaudal direction with the cerebral cortex and hippocampus being most sensitive [Auer et al, 1984]. Acute insulin-induced hypoglycaemia promotes a redistribution of regional cerebral blood flow and radioisotope labelled neuroimaging has shown that the blood flow to the frontal and parietal lobes increases during acute hypoglycaemia in non-diabetic adults [Tallroth et al, 1992]. Similarly, MacLeod et al [1994] reported increments in relative cerebral blood flow to both superior frontal cortices and the right thalamus, and significant decrements to the right posterior cingulate cortex and the right putamen in subjects with type 1 diabetes. The susceptibility of the frontal areas of the brain to hypoglycaemia has been shown by other tests, including electroencephalography [Harrad et al, 1985, Pramming et al, 1988, Tamburrano et al, 1988, Tallroth et al, 1990, Bendtson et al, 1991], and neuropsychological tests. The vulnerability of the frontal lobes to acute hypoglycaemia is important, as this part of the brain has been implicated in the performance of tasks requiring attention. Neuroimaging with Positron Emission Tomography (PET) in normal humans has provided evidence of neuro-anatomical localisation for these attentional processes. The blood flow to the frontal lobes is increased during the performance of many different tasks that require sustained attention [Deutsch et al, 1987, Cohen et al, 1988, Pardo et al, 1991]. Furthermore, adults who have sustained damage to their frontal lobes exhibit deficits on tasks that require sustained attention [Salmaso & Denes, 1982, Wilkins et al, 1987, Richer et al, 1993, Rueckert & Grafman, 1996]. With respect to selective attention, activation of the anterior cingulate gyrus of the frontal cortex has been demonstrated during performance of the Stroop Test [Pardo et al, 1990, Bench et al, 1993].



### **3.1.3 The Test of Everyday Attention**

The Test of Everyday Attention (TEA) is a cognitive test battery that gives a broad-based measure of the most important clinical and theoretical aspects of attention. It consists of eight subtests and can be used analytically to identify patterns of attentional breakdown. The TEA was devised from the evidence on separable attention systems in the brain [Posner & Peterson, 1990] and it was developed to improve existing methods of assessing attentional problems. The TEA attempts to measure aspects of the selection and vigilance systems of attention and correlates significantly with existing measures of attention [Robertson et al, 1994]. It gives a broad-based measure of the most important clinical and theoretical aspects of attention and can be used analytically to identify patterns of attentional breakdown. Moreover, it is the only test of attention based largely on everyday materials and the real-life scenario means that most patients enjoy the test and find it relevant. It yields standardised and reliable scores that allow valid comparisons in terms of selective attention, sustained attention and attentional switching.

During the standardisation and validation of the TEA, an age-, sex-, and IQ-stratified sample of 154 normal participants were given these tests, along with a number of existing tests of attention [Robertson et al, 1996]. The factor structure revealed by these data matched well contemporary evidence for a set of functionally independent attentional circuits in the brain, and included factors for sustained attention, attentional switching, selective attention and auditory-verbal working memory. The TEA was developed and standardised on the basis of these subtests, was shown to have high test-retest reliability, and correlated significantly with existing measures of attention [Robertson et al, 1996]. The discriminative validity of the TEA subtests has been confirmed in closed head injury patients [Chan et al, 2000].

The individual TEA subtests are described in detail in section 5.2.2.

## 3.2 INTELLIGENCE

### 3.2.1 General cognitive ability

Individuals differ from one another in their ability to understand complex ideas, to learn from experience, and to engage in various forms of reasoning. It is well recognised that differences in mental abilities have a hierarchical structure at the top of which rests *g*, or general cognitive ability [Carroll, 1993]. *g* is often the best practical predictor obtainable from a battery of mental tests accounting for up to half of the variance in test scores [Deary, 1998]. Spearman [1927a, 1927b], a British psychologist, in 1904, first noted that although a person may do relatively better on one subtest than another, those who score highly on one such subtest will likely be above average on others as well. Using factor analysis, these complex patterns can be clarified and a correlation coefficient – *r* – defined. The value of *r* measures the degree of relationship between two sets of scores, by assessing how well one of them could be used to predict the value of another. Spearman inferred that these correlations could be explained if there were some underlying common, or ‘general’ factor – *g* – in mental ability. Therefore, *g* refers to a statistical correlation, or a broad general factor that accounts for a portion of the variance of scores over a great variety of intellectual tasks.

However, while tests of general intelligence and *g* have high predictive values within the academic arena, their predictive validity becomes much smaller in other areas much more difficult to measure such as initiative, leadership and the ability to communicate effectively [Taylor, 1976, Guilford, 1977]. For example, tests of *g* have a predictive validity of around .3 in occupational performance, thus accounting for only about 10% of the variance [Cook, 1998, Hunter & Hunter, 1984].

Although the former discussion is relatively easy to grasp, there has been considerable debate among psychologists as to the true meaning of *g*. Therefore, Thomson in 1939 described it as a mere statistical regularity



[Thomson, 1939], Spearman as a 'kind of mental energy' [Spearman, 1927a, 1927b], and others as a generalised abstract reasoning ability [Gustafsson, 1984] or an index measure of neural processing speed [Reed & Jensen, 1992]. While alternative theories of intelligence exist, e.g. Gardner's theory of 'multiple intelligences' [Gardner, 1983] or Robert Steinberg's [1985] triarchic theory which proposes three fundamental aspects of intelligence – analytic, creative, and practical – the *g* based factor hierarchy is the most widely accepted current view of the structure of abilities, with *g* at the apex and various more specialised abilities arrayed beneath [Jensen, 1980].

Tests that correlate highly with *g* are complex, and require problem-solving analysis and rule inferring, such as Raven's Progressive Matrices [Raven, 1958]. The two main components of general cognitive ability that Raven sought to measure directly were previously identified by Spearman in 1923. These are eductive ability and reproductive ability. The Raven's Progressive Matrices are made up of a series of designs with a part missing, and measure eductive ability. The subjects taking the tests select the correct part to complete the designs from a number of options that are printed beneath. The Mill Hill Vocabulary Scale was designed to discriminate between people's knowledge of, and ability to replicate, verbal knowledge and concepts, and is a measure of reproductive ability.

### *Eductive ability*

The term eductive is derived from the Latin *educere*, which means 'to draw out' and refers to the ability to make meaning out of confusion, and to generate high-level, usually non-verbal, paradigms, which make it easier to handle complex situations and events. This is also known as 'fluid intelligence' and reflects the capacity to solve unfamiliar problems, i.e. the individual must approach a new problem (which more often than not is non-verbal in nature) in a novel way, and reach a solution quickly, analogous to thinking under pressure. These reflect the

abilities required by children in developing a sense of the unwritten rule of language.

To understand the concept of eductive ability, it is useful to examine how Spearman viewed this. Spearman noted that the initial detection of any problem requires a contextual perception. Therefore, when we approach a problem, we form a perceptual pattern or structure in our minds. This does not only apply to pictorial material because the immediate recollection after reading a piece of material is often only a concentrated awareness of its essence, rather than any of its parts. Next, if we are interested in the material, we may develop a sense of its implications in excess of its actual content. Following this we move on to analyse the condition, which may reveal a problem that needs to be solved, e.g. a part missing in the RPM. This analysis needs more than an overall perception of the problem; one has to be able to investigate and decide what is important to attend to within the problem as a whole. The RPM also measure the ability to deduce relationships, so that as each set of problems are presented the relationship of the past with the present has to be recognised to obtain the correct answer. Thus, eductive behaviour demands a perceptive process which involves problem solving after examining all the available preceding evidence. Importantly, such processes are often non-verbal, depending on flashes of insight which are often too rapid for assimilation into language. For example, Broadbent & Aston [1978] showed that the ability to manage a complex computer simulation of the British Economy was unrelated to the ability to answer questions on it.

### *Reproductive ability*

Reproductive ability, also known as crystallised intelligence, is the capacity to absorb, recall, and reproduce information that has been made clear and expressed between people. In other words, it replicates education- and experience-based knowledge; it tends to be a well-practised, highly learned knowledge, and is also likely to be largely verbal in nature.

However, although reproductive and eductive abilities are very different, they do interact considerably; perception and thought are generally dependent on acquired constructs, and the ability to absorb information is often dependent on being able to make meaning out of a confused area of discourse. In other words, eductive ability enables us to develop understanding, whereas the verbal competence of reproductive ability is needed to translate the understanding into words. Unsurprisingly, diffuse brain damage is far more likely to affect ‘fluid intelligence’ or eductive ability, than other aspects of cognition. By contrast, abilities that are concerned with stored information and knowledge, or reproductive ability, are more resistant to the effects of mild brain damage.

It is important to clarify a major point. Although the RPM are generally regarded as an excellent measure of *g*, this does not necessarily reflect general academic ability. The latter is defined by tests that assess the ability to recall factual information, i.e. tests of reproductive ability, rather than tests that measure critical thinking, judgement, or a readiness to find and sift through evidence. Therefore, people who can generate new insights and ideas may have difficulty verbalising these thoughts and concepts and hence struggle with standard tests of academic ability. Consequently, using the RPM to select students for academic subjects may not be appropriate because the chosen students may not excel in that type of subject. The next section briefly outlines the large body of research that has been performed on the Standard Raven’s Progressive Matrices over the last 70 years.

### **3.2.1 The Standard Raven’s Progressive Matrices**

#### *Standardisation of the RPM*

Following the introduction of the Standard RPM in the mid-1930s, it was revised and standardised in 1938 [Raven, 1941]. Extensive adult norms were collected during the Second World War, and the test was standardised on schoolchildren in 1943 [Raven & Walshaw, 1944]. Further data accrued on old people in the 1940s [Raven, 1948] and, during the Fifties and Sixties, checks

were run on the accuracy of norms [Adams, 1952]. Since then, local norming studies have been carried out in schoolchildren in various countries including Britain and Ireland, North America, Germany, New Zealand and Australia. Additional, new adult norms were collected in China and Belgium in the mid Eighties, and in Scotland and Iowa in the early Nineties. Therefore, the Standard RPM are an extensively studied and standardised test of cognitive ability [Raven et al, 1996].

#### *Reliability of the RPM*

Over forty studies dealing with the reliability of the RPM have been reported. In addition to studying normal populations, they cover a wide age-range, many cultural groups and clinical populations. Overall, the general picture is of good reliability, in terms of internal consistency and retest reliability. For example, in the 1979 British Standardisation of the RPM, the correlations between the item difficulties established separately for eight socio-economic groups ranged from .97 to .99 [Raven et al, 1996]. The correlations between the item difficulties established separately in the UK, US, Germany, New Zealand, and Chinese standardisations range from .98 to 1.00. Therefore, the RPM are extremely robust and measures the same factor in a wide range of cultural, socio-economic, and ethnic groups [Raven et al, 1996].

#### *Validity of the RPM*

The Standard RPM have shown reliable correlations with concurrent intelligence measures for English speaking children. For example, correlations of SPM with the Binet and Wechsler Scales, traditional measures of general intelligence, range from .54 to .86 [Raven et al, 1996]. Inter-test correlations for adult subjects are similar in magnitude and pattern to those outlined for children [Raven et al, 1996].

As previously noted, correlations between SPM and performance on achievement tests or academic achievement are generally lower than



correlations with intelligence tests, ranging from negligible to very high [Raven et al, 1996]. The Standard RPM are described in detail in section 5.2.3.

### **3.3 MOOD, CONATION (MOTIVATION) AND COGNITION**

#### **3.3.1 The Trilogy of Mind**

Psychology has traditionally identified and studied three components of mind; cognition, affect (mood) and conation (motivation). However, the distinction between cognition, conation and affection in psychology is regarded as a matter of emphasis rather than a true division because all human behaviour, especially learning and achievement, involves some mixture of all three aspects [Hilgard, 1980]. The interaction between these domains can be problematical because it may be difficult to differentiate the effects of mood from those of its cognitive and emotional components. For example, the effects of state anxiety on behaviour may be mediated by mood, e.g. tension, or by cognitions, e.g. intrusive thoughts and worries [Zeidner, 1998], or by motivations, such as the urge to withdraw from the threatening situation [Geen, 1987].

Briefly, cognition refers to the process of how we acquire and understand concepts, including encoding, storing, processing and retrieving that information. Affect refers to the emotional interpretation of perceptions, information or knowledge, and is generally associated with attachment, positive or negative, to people, objects or ideas. In the affective domain, mood states provide a background context for psychological functioning, and impinge on different functions such as memory and attention [Matthews, 1992]. In terms of an organisational structure within the trilogy of mind, conation is placed 'between' the cognitive and affective domains, with motivation and volition forming a continuum within the conative category [Kuhl & Beckman, 1994]. Traditionally, conation had received limited research attention because it is entwined within the study of other cognitive domains so it is difficult to separate [Snow, 1989]. For example, the Wechsler scales of intelligence include a conative component [Cooper, 1997, Gregory, 1998]. Generally, conation

reflects the motivational and volitional aspects of human behaviour. Motivation is an internal state or condition that serves to activate or strengthen behaviour and give it direction and refers to the intentional and personal motivation of behaviour [English & English, 1958]. Therefore, it is planned, deliberate and goal-oriented. It is a proactive, as opposed to reactive or habitual, aspect of behaviour [Emmons, 1986]. Conation is closely associated with the concept of volition, defined as the use of will, or the freedom to make choices about what to do [Kane, 1985]. For that reason, conation is absolutely critical if an individual is to successfully engage in self-direction and self-regulation.

### **3.3.4 The Dundee Stress State Questionnaire**

The Dundee Stress State Questionnaire (DSSQ) was developed as a comprehensive assessment of subjective states in performance contexts [Matthews et al, 1999]. It consists of 77 items that yield 10 factor-analytically determined scales under the headings of energetic arousal, tense arousal, hedonic tone, intrinsic task motivation, self-focused attention, self-esteem, concentration, confidence and control, task-relevant interference and task-irrelevant interference. The affective items within the DSSQ refer to diffuse moods, the motivation items to the pressures that instigate performance-related behaviour, and the cognitive items refer to self-referent beliefs and styles of thought. The instructions for the DSSQ emphasise the rating of immediate rather than typical subjective experience, thus ensuring reporting of states rather than traits [Matthews et al, 1999]. The main motivation dimension measured by the DSSQ relates to intrinsic motivation, which is the extent to which the person is motivated by interest and engagement in task content. Regarding the application of the DSSQ, the scales appear to have a variety of desirable psychometric properties including a sound factor-analytic basis, high internal consistency, moderate test-retest stability, and generality of properties across two Western cultures [Matthews et al, 1999].

The various components of the DSSQ are described in section 5.2.4.



## **CHAPTER 4**

### **HYPOTHESES FOR STUDIES**

#### **4.1 Acute hypoglycaemia and attentional dysfunction**

As described in Chapter 2, the effects of acute neuroglycopenia on cognitive function are well documented. However, the cognitive tests employed during these studies have been criticised for a lack of specificity and applicability to the activities of daily life undertaken by people with type 1 diabetes. Although it is well known that cognitive tests typically engage several putative mental processes, very little detailed information is available on the effects of controlled hypoglycaemia upon the specific information processing abilities of the brain. Therefore, it is recognised that further research needs to demonstrate that impairments in laboratory cognitive tasks have a bearing on mental performance in real life.

In study 1, 20 healthy volunteers were studied whereas in study 2, 16 subjects with type 1 diabetes were examined. A within subjects, counterbalanced test design examined the effects of acute hypoglycaemia on sustained attention, attentional switching, visual and auditory selective attention and auditory-verbal working memory. Although previous investigators have attempted to demonstrate attentional problems during acute hypoglycaemia using psychological tests, the data derived from these studies is the first to assess dysfunction of subdivisions of attention during hypoglycaemia using a test battery designed specifically to measure attention. The study hypothesis was that complex attentional tasks would deteriorate during hypoglycaemia, while simple tasks e.g. sustained attention, would be preserved.

#### **4.2 Does acute hypoglycaemia impair non-verbal reasoning?**

General intelligence is a key finding and theoretical construct in the psychometric structure of human abilities and is an important influence on many everyday activities. Although a deterioration in aspects of intelligence has been observed during acute hypoglycaemia, both in non-diabetic subjects [Stevens et al, 1989, McCrimmon et al, 1996] and in people with diabetes [Kerr et al, 1991b, Holmes et al, 1983, Ewing et al, 1998], few studies of non-diabetic or diabetic adults have included subtests that were designed specifically to measure aspects of non-verbal reasoning.

20 healthy volunteers (study 1) and 16 subjects with type 1 diabetes (study 2) are described. An identical study design examined the effects of acute hypoglycaemia on general fluid intelligence (non-verbal intelligence). An acknowledged key test of this ability (RPM) was used with the hypothesis that acute hypoglycaemia would lead to a significant deterioration in this important modality.

#### **4.3 Does motivation and subjective emotion moderate the degree of cognitive dysfunction during hypoglycaemia?**

Although many aspects of cognitive function have been examined during acute hypoglycemia, the subjective feelings that are generated by acute hypoglycemia experienced during task performance have not been studied. For example, style of thinking and beliefs, such as self-esteem, concentration, and control and confidence, in relation to tasks has not been examined (i.e. subjective cognition). Similarly, few studies have examined the non-cognitive changes in cerebral function that occur during acute hypoglycaemia including the influence on emotions (affect, mood). The conative aspect of mind has not been explored during hypoglycemia and no studies have examined either the role of motivation on the performance and outcomes of controlled studies of hypoglycemia, or the perception of workload during the tasks administered.

16 subjects with type 1 diabetes are described in study 3. Using a within subjects, counterbalanced test design, a validated test (DSSQ) measured mood, motivation and cognition before and after the transient stress of acute hypoglycaemia. This provided original data with the hypothesis that acute hypoglycaemia would have a negative impact on mood and motivation during these tests, thus allowing interpretation of the results of other such studies more broadly. In addition, it was surmised that acute hypoglycaemia would lead to a deterioration on subjective aspects of cognition.

#### **4.4 Post-prandial hypoglycaemia – effect of timing of insulin administration**

Insulin lispro is a fast-acting analogue of human insulin which is usually injected immediately before meals to avoid inducing preprandial hypoglycaemia. However, a delayed rise in postprandial blood glucose or a reduced magnitude of the glycaemic response to food may increase the risk of early postprandial hypoglycaemia.

12 subjects with type 1 diabetes were examined in study 4. The design was an open-label, randomised comparative study of the post-prandial glucodynamics of the insulin analogue, lispro, when administered either 5 minutes pre-prandially or 20 minutes after the commencement of a high fat/high solid phase meal. The aim of the study was to examine the effect of either pre- or post-prandial administration of insulin lispro on the pharmacodynamics of blood glucose following the consumption of a high fat, solid-phase meal, which is popular in the UK and is often consumed by many people with type 1 diabetes. The principal objective was to determine the optimal time of administration of insulin lispro in relation to a meal.



**Part II**  
**Methods**

## **CHAPTER 5**

### **METHODS**

## **5.1 GLUCOSE CLAMP STUDIES**

### **5.1.1 Subjects**

The details of criteria for selection of subjects for each study are explained in the individual chapters.

### **5.1.2 Ethical permission**

The Lothian Medicine Ethical Advisory Committee for Medicine and Clinical Oncology gave ethical permission for the studies. All subjects gave their written informed consent following a detailed explanation of the nature of the studies.

### **5.1.3 The hyperinsulinaemic glucose clamp technique**

In studies 1-3 hypoglycaemia was induced and maintained using a modified hyperinsulinaemic glucose clamp [DeFronzo et al, 1979]. This technique involves the continuous intravenous infusion of insulin at a fixed rate and a simultaneous 20% dextrose infusion at a variable rate. Insulin is initially infused at a rate of  $150 \text{ mU/m}^2/\text{min}$  before being reduced over a period of 10 minutes to a rate of  $60 \text{ mU/m}^2/\text{min}$ , at which it is maintained. This loading dose ensures saturation of the insulin receptors to facilitate subsequent manipulation of blood glucose. The infusion of 20% dextrose is commenced approximately 5 minutes after the insulin infusion is started, initially at a rate of about  $1 \text{ ml/kg/hr}$ . The subsequent rate of dextrose infusion is determined by the arterialised blood glucose concentration measured at the bedside every 5 minutes. In all the experiments, stable euglycaemia was achieved and then maintained at an arterialised blood glucose of  $4.5 \text{ mmol/l}$  for 30 minutes. Depending on the arm of the study being conducted, the dextrose infusion was then either maintained or altered to achieve euglycaemia or hypoglycaemia. To induce hypoglycaemia, the dextrose infusion was stopped for 5 minutes, then recommenced at half the rate required to maintain euglycaemia. This allowed the arterialised blood glucose concentration to decline smoothly over a 20-minute period to a level of  $2.6 \text{ mmol/l}$ . The dextrose infusion was then adjusted regularly for the duration of the experiment to maintain the predetermined level of hypoglycaemia. Blood

glucose was then maintained at the predetermined level for the duration of cognitive function testing, following which blood glucose was restored to normal.

#### **5.1.4 Experimental procedure**

Each session commenced at 0800 hrs after an overnight fast. The subjects with diabetes omitted their morning dose of insulin. Intradermal lignocaine (1%) was used for local anesthesia, and two cannulae were placed in the non-dominant arm, one being inserted retrogradely in a distal hand vein. This hand was used for blood sampling, having been placed in a warm blanket to 'arterialise' venous blood. A second intravenous cannula was placed in the antecubital fossa for infusion of 20% dextrose and human soluble insulin (Humulin S; Eli Lilly). After a brief priming regimen, insulin in supraphysiological concentrations was infused at a constant rate of 60 mU/m<sup>2</sup>/min into a peripheral vein using an IMED Gemini PCI pump. A variable infusion of 20% dextrose was given simultaneously via an IMED Gemini PCI pump and adjusted according to the blood glucose concentration measured at the bedside (Yellow Springs Instrument 2300 Stat, Yellow Springs, Ohio, USA). Samples of arterialised venous blood were obtained for glucose estimation initially at three-minute intervals, and then at five-minute intervals once a stable blood glucose concentration had been achieved.

In each study condition, the arterialised blood glucose concentration was stabilised at 4.5 mmol/l (baseline) for a period of 30 minutes, following which it was either maintained at 4.5 mmol/l (euglycaemia) or lowered to 2.6 mmol/l (hypoglycaemia). An arterialised blood glucose concentration of 2.6 mmol/l was chosen for the degree of hypoglycaemia to be tested because several previous studies have demonstrated significant impairment of various domains of cognitive function at this level [Deary et al, 1993a]. A period of 20 to 30 minutes elapsed between the baseline plateau and the attainment of hypoglycaemia to allow the blood glucose concentration to stabilise. The target

blood glucose concentration was maintained for a further 10 minutes before the tests were administered. Blood glucose was maintained at the study level for 90 minutes, during which the cognitive function tests and a questionnaire on the symptoms of hypoglycaemia were administered. Subjects were blinded as to the order of the studies and to their prevailing blood glucose concentration at all times throughout the procedure.

In the subjects with diabetes, HbA1c was measured by high-performance liquid chromatography (Variant II Hemoglobin Testing System; Biorad Diagnostics, Hercules, CA) (local DCCT-aligned non-diabetic reference range: 4.3-6.5%).

#### **5.1.5 Methodological limitations during studies of hypoglycaemia**

Despite the importance of studies designed to assess cognitive function and symptoms associated with experimentally induced hypoglycaemia, there are methodological limitations that need to be considered when interpreting the results of such studies. The supraphysiological levels of plasma insulin achieved using the hyperinsulinaemic glucose clamp technique do not readily mimic the pharmacological insulin concentrations that cause hypoglycaemia in patients with diabetes. Although glucose uptake into cerebral tissue was previously regarded as insulin-independent under physiological insulin concentrations [McCall, 1993], it is now known that the insulin-responsive glucose transporter, GLUT-4, is found in brain endothelial tissue [McCall, 1992]. Furthermore, insulin receptors have been identified in the brains of animals [Hill et al, 1986, Unger et al, 1989] and of humans [Hopkins & Williams 1997], especially in the hippocampus, hypothalamus and olfactory bulb. Therefore it is possible that the high concentrations of insulin, which prevail during the glucose clamp, could cause an artifactual rise in cerebral blood glucose uptake, and the physiological response including cognitive function during experimental hypoglycaemia may be different from the changes that occur during insulin therapy. However, it is hoped that the inclusion of a hyperinsulinaemic euglycaemia control arm in all the studies will control for any variables incurred. Although higher rates of



insulin infusion have been shown to attenuate the symptomatic and neuroendocrine responses to hypoglycaemia, it is reassuring that two human studies, in which differing concentrations of insulin were infused, did not affect the cognitive response to comparable levels of hypoglycaemia [Kerr et al, 1991a, Fanelli et al, 1994b].

Furthermore, such studies cannot be expected to reproduce exactly the conditions of clinical hypoglycaemia and the many extraneous modifying factors such as situation, activity and time of day. In addition, the perception of symptoms that patients have in a clinical situation is likely to differ from the perception that they report in response to probing questions during experimentally-induced hypoglycaemia. For example, knowledge of the imminence of experimentally-induced hypoglycaemia in non-diabetic subjects enhanced the intensity of neuroglycopenic symptoms, demonstrating the effect of anticipation on the perception of symptoms [Pohl et al, 1997].

One other important caveat should be recognised in studies of hypoglycaemia. When assessing the effects of hypoglycaemia on cognitive function it is important to ensure that 'arterialised' blood is sampled, reflecting the cerebral arterial glucose concentration. Warming the hand allows shunting of the blood from the arterial to the venous system and this arterialised venous blood has been shown to approximate very closely with true arterial blood glucose concentrations [Liu et al, 1992]. Knowledge of whether blood samples are plasma or whole blood, venous or arterialised are also important, both for comparing studies of hypoglycaemia and in the interpretation of the results, since glucose measurement of plasma gives a value around 10-20% higher than the equivalent concentration in whole blood [Foster et al, 1978].

## **5.2 COGNITIVE FUNCTION TESTS**

### **5.2.1 National Adult Reading Test (NART)**

The NART is widely used to estimate a person's premorbid level of intellectual ability, which is the peak level of mental ability achieved by an individual prior to any cognitive decline [Nelson, 1982]. The test requires subjects to read out loud a set of 50 words which are irregular in terms of their grapheme-phoneme correspondences, e.g. courteous, subtle. The responses are individually scored as correct or incorrect according to their pronunciation. This score can then be used to derive a premorbid IQ estimate. The NART has been validated against the Wechsler Adult Intelligence Scale and has been shown to correlate closely with this test in subjects without reason for cognitive decline [Crawford, 1992]. Furthermore, a recent retrospective validity study followed up 179 individuals that had been administered an IQ test at age 11. A comparison of these scores with the NART scores at age 77 lent strong support to the claim that NART estimates premorbid, rather than current intelligence [Crawford et al, 2001].

### **5.2.2 The Test of Everyday Attention (TEA)**

The absence of readily available paper and pencil tests for measures of subtypes of attention meant that relatively little was known about the clinical correlates of attention problems. The TEA was devised from the evidence on separable attention systems in the brain [Posner & Peterson, 1990] and it was developed to improve existing methods of assessing attentional problems. The TEA attempts to measure aspects of the selection and vigilance systems of attention and correlates significantly with existing measures of attention [Robertson et al, 1994]. It gives a broad-based measure of the most important clinical and theoretical aspects of attention and can be used analytically to identify patterns of attentional breakdown. Moreover, it is the only test of attention based largely on everyday materials and the real-life scenario means that most patients enjoy the test and find it relevant. It yields standardised and

reliable scores that allow valid comparisons in terms of selective attention, sustained attention and attentional switching.

The TEA is divided into eight subtests and has parallel forms [Robertson et al, 1994]. Subjects were asked to pretend that they were on holiday in Philadelphia in the USA, and were told that they would be asked to perform various tasks such as looking for symbols on maps and consulting telephone directories.

### *1. Map Search*

This is a test of selective attention. The subjects had to search for a particular symbol such as a sign that represented a garage, on a colour map – in this case of the Philadelphia area. The score is the number of symbols circled out of a possible maximum of 80 in two minutes. After the first minute had elapsed, the subjects were given a different coloured pen to circle the map signs, to enable the number of targets located in the first minute to be identified and compared to the final total achieved. This subtest loads on the same factor as the Stroop Test [Robertson et al, 1994]. A small proportion of subjects may have difficulty with this test because of visual acuity problems, but this can easily be assessed in preliminary fashion using the subtest map itself prior to embarking on the full test.

### *2. Elevator Counting*

This subtest was presented on audio-tape, and consisted of a simple counting procedure. Subjects were asked to pretend that they were in an elevator whose floor-indicator was not functioning. They had to ascertain at which 'floor' they had arrived by counting a series of tape-presented tones. Two practice items were provided at the beginning of the tape, so that the subjects were familiarised with the tones. This subtest is based on the procedure devised by Wilkins and colleagues that has been validated as a measure of right frontal lobe-based sustained attention [Wilkins et al, 1987]. The version used in the TEA is a variation of Wilkins' task as devised by Broks et al [1988] and loads on the

sustained attention factor of the factor analysis of data obtained from normal subjects.

### 3. *Elevator Counting with Distraction*

This subtest is similar to Elevator Counting, and was also presented on audio-tape. It differed in that subjects had to count the same tone that had been heard previously, while ignoring a distracting tone which had a higher note. The task commenced with two examples to demonstrate the difference between the two tones and to give the subject practice in counting.

### 4. *Visual Elevator*

In this subtest, the subject was asked to imagine that they were travelling up and down in an elevator, which in this case was represented by a series of pictures of elevator doors. Large arrows showed the direction of counting between pictures. This reversal task is a measure of attentional switching, and hence of cognitive flexibility. It is self-paced and the 'number correct' score loads on the same factor as the number of categories on the Wisconsin Card Sorting Test [Nelson, 1976].

### 5. *Elevator Counting with Reversal*

This subtest was the same as the visual elevator subtest except that it was presented at a fixed speed on audio-tape. It loads on the auditory-verbal working memory factor.

### 6. *Telephone Search*

In this test the subjects had to look for key symbols while searching through pages in a telephone directory. This subtest loads on the selective attention factor.

### *7. Telephone Search while Counting*

In this task, the subject had again to search for key symbols in a (different) telephone directory while simultaneously counting a series of strings of tones presented on audio-tape. By combining the scores for this subtest, and the time per target score for the previous telephone search, this test aims to provide a measure of divided attention, a 'dual task decrement'. In the factor analysis of normal data, this task loads on the sustained attention factor.

### *8. Lottery*

In this final subtest of sustained attention, subjects had to listen for their (predetermined) winning lottery numbers. To do this, they had to listen to a 10 minute series of audio-tape-presented numbers of the form 'BC143', i.e. two letters followed by three numbers. The task was to write down the two letters preceding all lottery numbers ending in certain numbers, e.g. '55'.

The ability to select target stimuli, while not selecting powerfully competing distractors, seems to be the common factor uniting the different tests of selective attention (table 5.1). Subjects who have a visual selective attention deficit may have difficulty filling out forms, looking up transport timetables/TV schedules, or finding what they are looking for on supermarket shelves. The visual elevator subtest measures attentional switching and this test is sensitive to problems of flexibility of thought and would reflect difficulties in changing from one topic to another, e.g. during a meeting. Subtests loading on the sustained attention factor involve the ability to sustain attention to repetitive stimuli in the absence of external cues to attend (lottery counting and elevator counting). People who do poorly on these tasks find it difficult to keep their mind on a relatively dull, unchanging task. They may also lose concentration while reading or watching television, and even while talking with friends and family. The telephone search while counting subtest involves a strong sustained attention factor, but also measures divided attention, and it is likely that the former is an important factor in dual task performance, i.e. remembering to



attend to the second task while engrossed in the first. This test is highly sensitive to the ability to handle the complex demands of everyday life. For example, making a meal and holding a conversation simultaneously. The elevator counting with reversal and elevator counting with distraction subtests involve the manipulation and sequencing of auditory-verbal information in working memory and also measure auditory selective attention. Subjects who have difficulties with these tests may have problems with complex mental arithmetic, or working out other problems mentally.

The tests were carried out in a quiet, well-lit area with a flat surface on which visual test materials could be placed. Verbatim instructions were given for all subtests, as well as background information for each subtest. The maps and telephone directory materials were encased in clear plastic which the subjects could mark with water-based colour pens. After scoring at the end of the test session, the plastic could be wiped with a damp sponge to make it ready for the next subject.

**Table 5.1** TEA subtests and their attentional correlates. Reproduced from *Diabetic Med* 2006; 23: 26-31 with permission of Blackwell Science Ltd. Copyright 2006, Blackwell Science Ltd

Attentional Process	Test
Selective Attention	Map Search
Speed Of Information Processing	Telephone Search
Attentional Switching	Visual Elevator
Sustained Attention	Lottery Counting Elevator Counting Telephone Search While Counting
Divided Attention	Telephone Search While Counting
Attentional Switching	Elevator Counting With Reversal Elevator Counting With Distraction

During the scoring of the TEA, account had to be taken of age when interpreting each subtest score. This was done by looking up a subject's score in one of four separate age categories. The role of verbal intelligence in scoring is sufficiently low as to be relatively unimportant in interpreting scores and there are no sex differences or adjustments required for gender in any of the subtests.

### **5.2.3 Raven's Progressive Matrices (RPM)**

Within the psychometric study of intelligence, general fluid intelligence reflects adaptive, problem-solving ability, and is largely non-verbal in nature. Raven's Progressive Matrices [Raven's Progressive Matrices, SPM, 1958] is a test of non-verbal reasoning that involves rule induction and application in abstract patterns. It is closely associated with general fluid intelligence [Marshalek et al, 1983]. General intelligence is a key finding and theoretical construct in the psychometric structure of human abilities [Carroll, 1993], and is an important influence on the quality of performance of many everyday activities [Gottfredson, 1997]. The RPM are considered to be the single best test of general fluid intelligence [Marshalek et al, 1983].

When the RPM were designed, Raven set out to develop tests that would be easy to administer and to interpret in a clear, theoretical way [Raven, 2000]. The Matrices' items are diagrammatic puzzles exhibiting serial change in two dimensions simultaneously. Each puzzle has a part missing which the subject has to find among the answer options provided. The correct answer is found by discovering and correctly applying the rules governing the changes in each item's pattern. The test consists of 60 items divided into five sets (A, B, C, D, E), each consisting of 12 items. In each set the first puzzle is very easy. The puzzles that follow build on the argument of those that have gone before and become progressively more difficult. Therefore, each problem in the set is really the source of a system of thought. The order of the items provides the standard training in the method of working and the five sets provide ample opportunity to grasp the method of thought required to solve the problems. All

of the problems are boldly presented and accurately drawn to ensure sustained interest and freedom from fatigue. It is generally not possible to solve the more difficult problems of the RPM if the capacities to solve the easier problems are not present. Evidence for this is derived from the Item Characteristic Curves plotted when the test was being developed and re-run in the course of a number of subsequent standardisations. As a result, three facts were derived from this data. Firstly, that all the items were measuring a common factor. Secondly, that the abilities that are required to solve the more difficult problems form part of a range which starts with the easiest items. Finally, although the abilities that are required to solve the more difficult problems may appear to be qualitatively different from those required to solve the easier ones, these apparently different abilities shade imperceptibly one into the other [Raven et al, 1996].

Subjects were assigned two scores for this test; the number correct at 20 minutes and the number correct at completion (no time limit). By doing this, the speed of accurate intellectual work and the total capacity for orderly thinking of each subject could be assessed. However, subjects were instructed to work at their own pace and not to be concerned with a time limit. This was important because as the five sets of items forming the test each begins with easy problems and end with difficult ones, the scores would not be reliable if a single time limit was used which did not allow everyone to finish. This is because a subject's score would be very different if time ran out while they were working on the difficult problems of an early set, rather than a few moments later, when they would be moving quickly through the easier items of the next set. It is important to note the strengths and weaknesses of the RPM. Strengths include that it can be used with respondents of all ages from early childhood to the elderly and it is of a duration that it can be applied in many different situations, such as home, school or the laboratory. However, it does have limited discrimination at the upper and lower levels of ability [Raven et al, 1996].

#### **5.2.4 Dundee Stress State Questionnaire (DSSQ)**

The application of the DSSQ to the study of hypoglycemia is novel. It aims to be a comprehensive, multi-dimensional assessment instrument for transient mental states associated with stress, arousal and fatigue [Matthews et al, 1999]. The DSSQ seeks to measure state dimensions within the three traditional psychological domains of affect (mood), motivation (conation), and cognition. It consists of 10 factor analytically determined scales, which load onto three secondary factors that reflect the individual's stress state. Three of the scales reflect Task-Engagement (energetic arousal, motivation, and concentration), three scales constitute the dimensions of Distress (tense arousal, confidence and control, and hedonic tone), and four scales define the dimension of Worry (self-focused attention, self-esteem, task relevant cognitive interference, and task-irrelevant interference). There are two versions of the test: Annexe A is administered prior to task performance, and Annexe B is completed after the task. In the pre-task assessment, subjects are informed that the questionnaire will assess their feelings and thoughts at that moment in time. In Study 3, Annexe A of the DSSQ was administered before the TEA. After the task, subjects are given a further questionnaire that asks them about the thoughts and feelings they experienced while they were performing the task. In Study 3, Annexe B was given after the RPM. Instructions for the DSSQ emphasise rating immediate rather than typical subjective experience, to ensure reporting of short-term states rather than enduring traits. The latter is a personality disposition that shows much greater temporal stability [Matthews et al, 2003].

The mood dimensions of the DSSQ are subdivided into energetic arousal, tense arousal and hedonic tone. The motivation dimension relates to intrinsic motivation, i.e. the extent to which the person is motivated by interest and engagement in task content. Cognitive dimensions assess self-referent beliefs and styles of thought including task-related and task-irrelevant interference, self-focus of attention, which refers to a state of self-preoccupation and reflection, or private self-consciousness, and self-esteem, which refers to sets of beliefs about



self-worth, especially as evaluated by others. Concentration items refer to attention to the task being undertaken, and resisting distraction whereas confidence refers to beliefs about personal control and success in task performance.

The DSSQ comprises a compendium of existing scales and items for important stress-related constructs that are not adequately accommodated by other questionnaires. Subjects were given a series of four DSSQ questionnaires under the following headings:

1. Uwist Mood Adjective Checklist (UMACL)
2. Motivation and Workload
3. Thinking Style
4. Thinking Content.

Each questionnaire tested a particular domain through a specific series of questions or items. No more than 8 items were selected for each scale.

#### *DSSQ Affect*

Part 1 of the DSSQ questionnaires is the UWIST Mood Adjective Checklist [Matthews et al, 1990a], which is used to index three dimensions of energy, tension and hedonic tone. The checklist has been validated in both experimental studies [Matthews et al, 1990b] and in field studies of real world stressors [Matthews et al, 1991]. The adjectives used to characterise the mood dimensions which were included in this questionnaire were graded by intensity on a scale of 1 to 4 and were classified into three groups: hedonic tone, tense arousal and energetic arousal. Higher scores indicate a higher happiness rating for hedonic tone, a high anxiety rating for tense arousal, and a high energy rating for energetic arousal. Using this questionnaire, the maximum score that can be obtained for each of the three mood components is 32, and the minimum score is 8.



### *DSSQ Motivation and Workload*

Part 2 of the DSSQ questionnaires deals with motivation and workload. The items in this task represent two major aspects of motivation in performance settings; task interest and aspiration to achieve successful performance. In the pre-task questionnaire, subjects were asked 8 questions about their attitude to the task that they were about to undertake e.g. "How eager are you to do well at the task". They graded their answers on a Likert scale ranging from zero (Not at all) to 9 (A great deal). In the post-task questionnaire, they were asked a similar series of questions to assess attitude to the task just completed. The maximum score that can be obtained is 72 and the minimum score possible is 0. The subjects then proceeded to complete an additional six questions to rate the mental, physical and temporal demand of the task completed, the effort put into the task, and their perceived rating of performance and frustration with the task. These are rating scales derived from the NASA-TLX [Hart & Staveland, 1988], each assessing a different aspect of the workload imposed by the task. The maximum score that can be obtained for workload is 60 and the minimum score possible is 0.

### *DSSQ Cognition*

Part 3 of the DSSQ questionnaires ('Thinking Style') assesses the person's general style of thinking and beliefs about the task. It is important to note that this is not cognitive performance; rather, it is self-reported beliefs about one's cognitive performance. Existing, validated measures were used to assess cognitive interference from the task itself and from personal concerns [Sarason et al, 1986], performance and social self-esteem [Heatherton & Polivy, 1991], and self-focus of attention [Fenigstein et al, 1975]. This aspect of the questionnaire assessed self-focused attention (8 items), self-esteem (7 items), concentration (7 items), and control and confidence (6 items) by a series of 28 questions. Subjects were asked a series of statements about their thoughts at that moment (pre-task questionnaire) and during the task (post-task questionnaire). For example, a question relating to self-esteem would be "I am

worried about whether I am regarded as a success or failure” and answers were graded on a Likert scale from zero (Not at all) to 4 (Extremely).

Part 4 of the DSSQ questionnaires examined ‘Thinking Content’ and comprised items from the Cognitive Interference Questionnaire [Sarason et al, 1986], which evaluates task-related interference (8 items) and task-irrelevant interference (8 items). For example, a question from the former would be “I thought about how much time I had left” and from the latter “I thought about personal worries”. Scores were graded on a Likert scale from 1 (Never) to 5 (Very often).

### **5.3 Symptoms of hypoglycaemia**

A subjective self-rating system (The Edinburgh Hypoglycemia Scale) [Deary et al, 1993a] was used at four time points; baseline, before and after the TEA, and after the RPM. The symptoms of hypoglycaemia were classified as autonomic (palpitations, sweating, shaking and hunger), neuroglycopenic (confusion, drowsiness, inability to concentrate, speech difficulty and blurred vision) and non-specific (nausea and headache). Each symptom was graded on a Likert scale of 1 to 7 (1 = not present, 7 = very intense). The total for each subgroup of hypoglycaemic symptoms was calculated.

### **5.4 Statistical analysis**

The statistical methods used in each of the studies are described in the individual chapters. A p value of less than 0.05 was considered to be significant. In the glucose clamp studies, with 16 subjects and a repeated measures design, the power of the study in detecting a 0.5 standard deviation change (medium effect size) in any test (assuming  $\alpha=0.05$ , reliability of test=0.8) was 94%. Using the same assumptions, the power of detecting a 0.33 standard deviation change (small-medium effect size) was 63%.

Effect size was calculated using Eta squared ( $\eta^2$ ).  $\eta^2$  is the proportion of the variance in the test scores accounted for by study condition (euglycaemia vs. hypoglycaemia). A  $\eta^2$  score of 0.25-0.5 was considered a moderate effect size [Cohen, 1992]. All analyses were performed using SPSS version 11.0 for Windows.

### **Part III**

#### **Studies involving acute insulin-induced hypoglycaemia**

## **CHAPTER 6**

### **STUDY 1**

#### **ATTENTIONAL FUNCTIONING IS IMPAIRED DURING ACUTE HYPOGLYCAEMIA IN HUMANS**



## 6.1 Introduction

As discussed in Chapter 2, the human brain is dependent on glucose for its oxidative metabolism, and hypoglycaemia rapidly causes impairment in brain functioning through the effects of acute neuroglycopenia [Deary, 1993b]. This has been demonstrated in numerous studies using a variety of neuropsychological [Holmes et al, 1983, 1984, Pramming et al, 1986, Heller et al, 1987, Hoffman et al, 1989, Stevens et al, 1989, Widom & Simonson, 1990, Mitrakou et al, 1991, Cox et al, 1993b, Mellman et al, 1994] and neurophysiological tests [Pramming et al, 1988, Tamburrano et al, 1988, Blackman et al, 1990, Jones et al, 1990, Tallroth et al, 1990, Zeigler et al, 1992]. Tasks which involve higher cognitive processes are thought to be more sensitive to neuroglycopenia than motor tasks [Cox et al, 1993b]. In addition, tasks that involve rapid responses and those which are more cognitively complex and attention demanding tend to show substantial impairment during neuroglycopenia whereas simple motor tasks and cognitive tasks such as digit span, finger tapping and simple reaction times are relatively well preserved [Deary, 1993b]. Although it is recognised that cognitive function is impaired during hypoglycaemia, it is not clear which basic brain processes are affected by neuroglycopenia, nor is it known to what extent neuropsychological tests, which typically engage several putative mental processes, index abilities of cognitive functioning that are important in everyday life. Because cognitive abilities are important for work and leisure activities, this information is of considerable practical as well as theoretical importance.

Attention is a complex mental ability involving multiple subcomponent processes [Posner & Peterson, 1990], and several independent attention systems in the brain serve different functions. Although no dominant theory can integrate all of these components within a unifying framework, several models have been proposed that support the concept of fractionation of attention into different supramodal systems each of which has a distinct neuroanatomical basis [Posner & Peterson, 1990].

Because attention is a fundamental cognitive process that is integral to many neuropsychological tests, the examination of attentional dysfunction is difficult to study in isolation. The attentional processes that have been studied most frequently involve focusing, selecting, dividing, sustaining, suppressing, and inhibiting attention. Classical neuropsychological tests purporting to assess attention have deteriorated during controlled hypoglycaemia in non-diabetic subjects [Mittrakou et al, 1991, Stevens et al, 1989], and in adults with type 1 diabetes [Holmes et al, 1984, Pramming et al, 1986, Widom & Simonson, 1990]. However, little detailed information is available on the effects of controlled hypoglycaemia upon the brain's specific information processing abilities, and further research needs to demonstrate that impairments in laboratory cognitive tasks have a bearing on mental performance in real life. Furthermore, we need a study using a validated batch of attention tests during hypoglycaemia.

As a major construct within the psychometric study of intelligence, fluid intelligence reflects adaptive, problem-solving ability, and is largely non-verbal in nature. The Raven's Progressive Matrices [Raven's Progressive Matrices, SPM, 1958] are an acknowledged key test of this ability. General intelligence is a key finding and theoretical construct in the psychometric structure of human abilities [Carrol, 1993], and is an important influence on many everyday activities [Gottfredson, 1997]. Few previous studies of acute hypoglycaemia have included subtests that were designed specifically to measure aspects of intelligence and it is surprising that such a test has not been utilised previously in the study of hypoglycaemia in humans. In a previous study, mathematical computations were impaired at a venous blood glucose level of 3.3 mmol/l in 12 patients with type 1 diabetes, but reading comprehension was not affected [Holmes et al, 1983]. The Digit Symbol Task, a subtest of the Weschler battery of intelligence tests (WAIS-R) [Weschler and Stone, 1981] was impaired at arterialised blood glucose concentrations ranging from 2.5 mmol/l to 3.4 mmol/l

[Stevens et al, 1989, McCrimmon et al, 1996] in non-diabetic human volunteers, and at 2.8 mmol/l in subjects with diabetes [Kerr et al, 1991b].

Therefore, the aim of the present study was to examine the effects of acute controlled, insulin-induced hypoglycaemia on general fluid intelligence and on different aspects of attention using validated tests.

## **6.2 Research Design and Methods**

### *Subjects*

Twenty (9 male) healthy volunteers were studied. Their mean (SD) age was 28.7 (5.3) years with a mean (SD) Body Mass Index of 23.7 (1.9) kg/m<sup>2</sup>. The mean (SD) National Adult Reading Test (NART) number correct score was 28.9 (5.8). The subjects did not have a previous medical history or a family history of diabetes, previous head injury or psychiatric disorder. They had no intercurrent illness and none were taking medications (other than the combined oral contraceptive pill). Subjects were not paid to participate in the study other than travel expenses. The protocol was approved by the Healthy Volunteer Studies Medical Research Ethics Sub-Committee of the Lothian Medicine and Oncology Ethical Advisory Committee. All subjects gave written informed consent for study.

### *Study Design*

The study design is shown in figure 6.1. Subjects were studied on two occasions, separated by at least one week, in a counterbalanced order, i.e. half of the subjects underwent the euglycaemia session first, followed by the hypoglycaemia study, and the other half were studied in the reverse order. A



modified hyperinsulinaemic glucose clamp technique was used [De Fronzo et al, 1979] to set the blood glucose at a predetermined level. In one condition, hypoglycaemia was induced (blood glucose 2.6 mmol/l), and in the other condition, euglycaemia, the blood glucose concentration was maintained at 4.5 mmol/l. During the two study conditions (euglycaemia and hypoglycaemia) the subjects were asked to complete tests of cognitive function and a questionnaire of the symptoms of hypoglycaemia. Subjects were blinded to the order of the studies and to their prevailing blood glucose concentration at all times throughout the procedure.

### *Procedure*

A modified hyperinsulinaemic glucose clamp technique was used, in which insulin was infused, in supraphysiological concentrations, at a constant rate into a peripheral vein to lower the blood glucose progressively, as detailed in section 5.1.4.

### *Cognitive Function Tests*

During the euglycaemia and hypoglycaemia arms of the study subjects were administered the Test of Everyday Attention (TEA) [Robertson et al, 1994] followed by the Raven's Progressive Matrices (RPM) [Raven's Progressive Matrices, SPM, 1958]. The order of the tests was identical during each study condition.

### **Test of Everyday Attention (TEA)**

The TEA has been described in detail in section 5.2.2. Briefly, the TEA is divided into eight subtests that aim to assess selective, sustained and attentional switching. In the present study, the subjects were asked to pretend that they were visiting Philadelphia in the USA, and were told that they would be asked to perform various tasks such as looking for symbols on maps and consulting telephone directories.



### **Raven's Progressive Matrices (RPM)**

The RPM was used to examine fluid intelligence and is detailed in section 5.2.3. The Standard and Parallel forms of the Matrices were administered after the TEA was completed. Subjects were assigned two scores for this test; they were asked to circle the number of the question they were attempting at 20 minutes and then allowed to continue with the test until completion, so introducing a time component.

### ***Symptoms of hypoglycaemia***

The Edinburgh Hypoglycaemia Scale [Deary et al, 1993a] was administered at four time points; baseline, before and after the TEA, and after the RPM (figure 6.1). The symptoms of hypoglycaemia were classified as autonomic (palpitations, sweating, shaking and hunger), neuroglycopenic (confusion, drowsiness, inability to concentrate and blurred vision) or non-specific (nausea and headache). Each symptom was graded on a Likert scale of 1 to 7 (1 = not present, 7 = very intense). The total for each subgroup of hypoglycaemic symptoms was calculated.

### ***Statistical analysis***

The results were analysed independently for each subtest of the TEA and the RPM. A general linear model repeated measures analysis of variance was used with order of session as a “between-subjects” factor with two levels (euglycaemia-hypoglycaemia or hypoglycaemia–euglycaemia), and condition as a “within subjects” factor with two levels (euglycaemia versus hypoglycaemia). A similar model was used to analyse the symptoms of hypoglycaemia, with the addition of time as a “within-subjects” factor with four levels. During the symptoms analysis, the principal outcome statistic was any (experimental versus time) interaction as this indicated the effects of hypoglycaemia on symptoms controlled for day-to-day variation by including baseline scores. A p value of less than 0.05 was considered to be significant. All analyses were performed using SPSS version 10.0 for Windows.

### 6.3 Results

The mean (SD) fasting venous blood glucose was 4.3 (0.3) mmol/l and did not differ between the two study days. Stable blood glucose plateaux were achieved during both conditions (figure 6.2). The mean (SD) blood glucose concentration during the hypoglycaemia clamp was 2.6 (0.2) mmol/l, and during euglycaemia was 4.5 (0.2) mmol/l. The initial statistical analysis revealed that no significant order effects (asymmetrical transfer effects) had occurred for any of the outcome variables in this study, other than the “elevator counting with reversal” task.

#### *Symptoms*

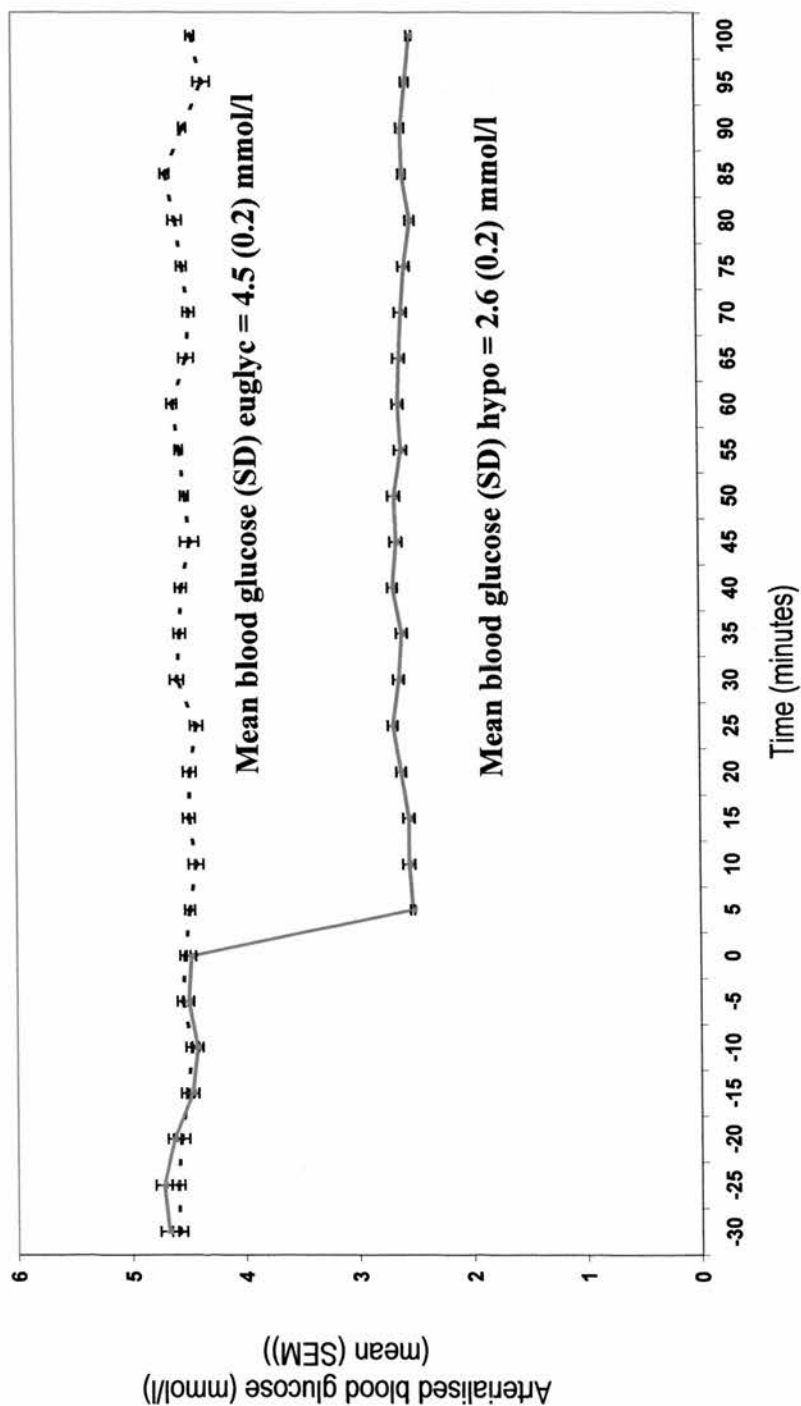
Significant increments were observed in the autonomic ( $p=0.001$ ) and neuroglycopenic ( $p=0.02$ ) scores during hypoglycaemia (table 6.1). There were no significant changes on malaise scores ( $p=0.1$ ). The significant increments in neuroglycopenic and autonomic symptom reports confirmed that the subject group had symptomatic awareness of hypoglycaemia at the predetermined low blood glucose concentration and, more specifically, were experiencing neuroglycopenia.

**Table 6.1** Symptom scores during hypoglycaemia in 20 non-diabetic volunteers

	<b>Euglycaemia</b>		<b>Hypoglycaemia</b>		<b>p value</b>
	Baseline	End study	Baseline	End study	
<b>Autonomic</b>	5.4 (1.6)	5.3 (1.6)	5.5 (1.6)	13.3 (5.0)	0.001
<b>Neuroglycopenic</b>	4.9 (1.6)	5.3 (2.0)	5.5 (1.8)	9.9 (4.9)	0.02
<b>General malaise</b>	2.3 (0.6)	2.4 (0.6)	2.1 (0.52)	3.3 (1.6)	0.1

Values are means (SD)

P value refers to the interaction of ‘experimental condition versus time’ in ANOVA



**Figure 6.2** Blood glucose profiles during euglycaemia and hypoglycaemia in 20 non-diabetic volunteers. Values are shown as mean (standard error of the mean)

### *Tests of Attention*

The results of the visual selective attention and auditory selective attention tests are summarised in table 6.2. Table 6.3 contains the results for attentional switching, sustained attention and divided attention.

#### *Visual Selective Attention*

Acute hypoglycaemia caused a significant deterioration in tests sensitive to a visual selective attention deficit. The mean number (SD) of map symbols circled during euglycaemia in one minute was 46.1 (10.0) versus 39.9 (10.2) during hypoglycaemia ( $p=0.009$ ,  $\eta^2=0.32$ ). The mean number (SD) of symbols circled in two minutes was also lower at 68.1 (11.3) during hypoglycaemia, compared with 71.8 (6.9) in the euglycaemia condition, but did not achieve statistical significance ( $p=0.1$ ). In the telephone search task, no difference was demonstrated between euglycaemia and hypoglycaemia in the number of symbols located. However, the mean (SD) time taken to complete the task increased from 51.7 (7.3) seconds during euglycaemia, to 57.0 (11.2) seconds during hypoglycaemia ( $p=0.005$ ,  $\eta^2=0.32$ ). Furthermore, the telephone search raw score, or the number of symbols located per second, increased from 2.7 (0.4) during euglycaemia, to 3.1 (0.7) during hypoglycaemia ( $p=0.005$ ,  $\eta^2=0.36$ ) (figure 6.3). The results demonstrate that a visual selective attention decrement had developed during hypoglycaemia.

#### *Auditory Selective Attention/Auditory Verbal Working Memory*

With the auditory elevator test with distraction, the achieved score declined from a mean (SD) of 9.2 (1.2) during euglycaemia to 7.8 (2.0) during hypoglycaemia ( $p=0.003$ ,  $\eta^2=0.40$ ). By contrast, the score attained on the elevator test with reversal, did not deteriorate during hypoglycaemia, with a mean (SD) score of 7.3 (2.6) during euglycaemia compared to 7.1 (2.3);  $p=0.7$  during hypoglycaemia. A significant order effect occurred with this test ( $p=0.01$ ,  $\eta^2=0.28$ ). When subjects went through the euglycaemia arm of the study first, the score increased from 5.8 (euglycaemia study day) to 6.4

(hypoglycaemia study day). By contrast, an initial hypoglycaemia study day demonstrated a decrease in scores from 8.8 to 7.9 (euglycaemia study day).

### *Sustained Attention*

Sustained attention did not deteriorate during hypoglycaemia using either the lottery ticket test ( $p=0.2$ ) or the elevator counting test ( $p=0.1$ ).

### *Attentional Switching*

In the visual elevator task, no difference was observed in the raw score between the two study conditions. The mean (SD) raw score during euglycaemia was 9.1 (1.3) compared with 8.8 (1.6) during hypoglycaemia ( $p=0.4$ ). However, during hypoglycaemia a longer time was required to complete the visual elevator task with a mean (SD) time of 136.9 (22.2) seconds, compared to 112.7 (15.0) seconds during euglycaemia ( $p<0.0001$ ,  $\eta^2=0.76$ ), which was a highly significant difference (figure 6.3).

### *Divided attention*

In the task that involved search of a telephone directory while counting, no significant difference was observed in the number of symbols that were located during either study condition. The time taken to complete the task was higher during hypoglycaemia with a mean (SD) of 60.0 (14.6) seconds compared to 55.9 (9.5) seconds during euglycaemia, but this difference was not significant ( $p=0.1$ ). The time per target score, which is the ratio of the number of circled symbols divided by the time taken for the task, was higher with a mean (SD) of 3.4 (0.6) targets/second during hypoglycaemia compared to 3.1 (0.8) targets/second during euglycaemia ( $p=0.02$ ,  $\eta^2=0.26$ ). The dual task decrement was not significantly different between the two conditions ( $p=0.2$ ).

### *Fluid intelligence*

Using Raven's Progressive Matrices, no significant differences were observed between euglycaemia and hypoglycaemia in the scores achieved either at 20



minutes or upon completion of the test (figure 6.4). The mean (SD) RPM score at 20 minutes was 48.4 (5.7) during euglycaemia and 47.2 (5.1) in the hypoglycaemia condition ( $p=0.1$ ). Upon completion, the mean (SD) score was 49.5 (5.6) in the euglycaemia condition and 48.7 (4.9) during hypoglycaemia ( $p=0.3$ ). No significant differences were found between the two study conditions in the times taken to complete the test.

**Table 6.2** Selective attention during euglycaemia and hypoglycaemia in healthy volunteers (n=20). Reproduced from *Diabetes Care* 2001; 24: 1745-50 with permission of the American Diabetes Association. Copyright 2001, American Diabetes Association

<i>Attentional system</i>	<i>Subtest</i>	<i>Euglycaemia</i>	<i>Hypoglycaemia</i>	<i>p value</i>	<i>η<sup>2</sup></i>
<b>Visual selective attention</b>	Map search symbols in one minute	46.1 (10)	39.9 (10.2)	0.009	0.32
	Map symbols circled in two minutes	71.8 (6.9)	68.1 (11.3)	0.1	0.12
	Telephone search time (secs)	51.7 (7.3)	57.0 (11.2)	0.005	0.36
	Telephone search correct symbols	18.8 (1.3)	18.8 (1.4)	0.8	0.001
	Telephone search raw score (time/target)	2.7 (0.4)	3.1 (0.7)	0.005	0.36
<b>Auditory selective attention</b>	Elevator counting with distraction	9.2 (1.4)	7.8 (2.0)	0.003	0.40
	Elevator counting with reversal	7.3 (2.6)	7.1 (2.3)	0.7	0.01

Values are mean (SD)  
η<sup>2</sup> is the proportion of the variance in the test scores accounted for by study condition (euglycaemia vs hypoglycaemia)

**Table 6.3** Attentional function during euglycaemia and hypoglycaemia in healthy volunteers (n=20).  
 Reproduced from *Diabetes Care* 2001; 24: 1745-50 with permission of the American Diabetes Association. Copyright 2001, American Diabetes Association

<i>Attentional system</i>	<i>Subtest</i>	<i>Euglycaemia</i>	<i>Hypoglycaemia</i>	<i>p value</i>	<i>η<sup>2</sup></i>
<b>Attentional switching</b>	Visual elevator raw score	9.1 (1.3)	8.8 (1.6)	0.4	0.03
	Visual elevator timing score (secs/switch)	3.0 (0.6)	3.6 (0.5)	<0.0001	0.69
	Visual elevator time (secs)	112.7 (15.0)	137.9 (22.6)	<0.0001	0.76
<b>Sustained attention</b>	Elevator counting	6.9 (0.3)	6.8 (0.4)	0.1	0.03
	Lottery tickets	9.4 (1.0)	9.1 (1.5)	0.2	0.08
<b>Divided attention</b>	TSWC time (secs)	55.9 (9.5)	60.0 (14.6)	0.1	0.13
	TSWC correct symbols	18.3 (1.9)	17.6 (2.2)	0.2	0.07
	TSWC time /target score	3.1 (0.8)	3.4 (0.6)	0.02	0.26
	Dual task decrement	0.8 (0.9)	0.7 (0.7)	0.2	0.01

Values are mean (SD)  
 η<sup>2</sup> is the proportion of the variance in the test scores accounted for by study condition (euglycaemia vs hypoglycaemia)  
 TSWC – Telephone Search While Counting

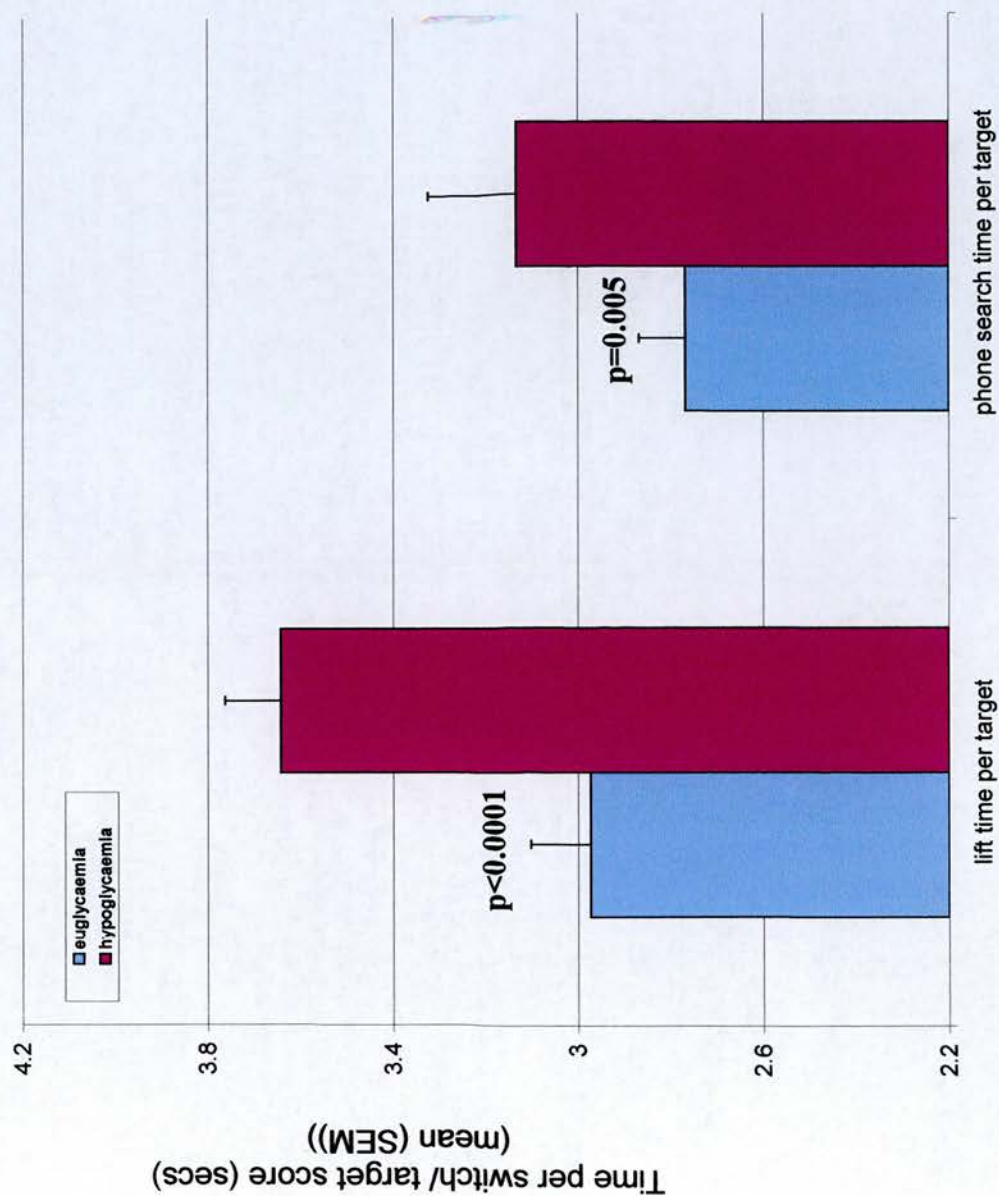
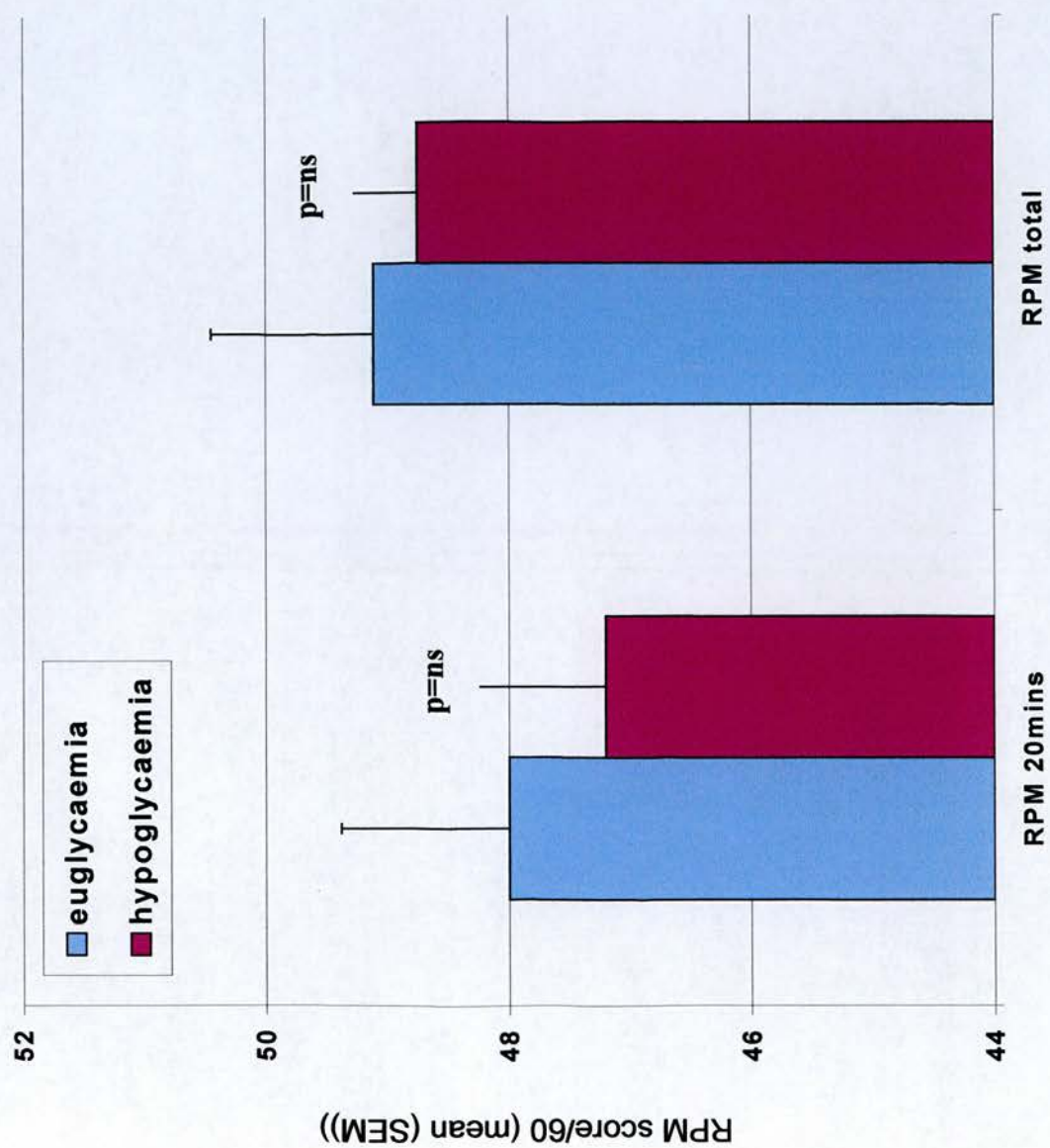


Figure 6.3

Attentional deficits during hypoglycaemia. Data derived from McAulay et al, 2001



**Figure 6.4**

Results for Raven's Progressive Matrices in 20 non-diabetic volunteers. Data derived from McAulay et al, 2001



## 6.4 Discussion

The present study has demonstrated that controlled hypoglycaemia in non-diabetic humans causes attentional dysfunction. A decline in the rate of information processing was demonstrable in visual and auditory selective attention, and in attentional switching. By contrast, fluid intelligence was not affected by hypoglycaemia. An arterialed blood glucose concentration of 2.6 mmol/l was chosen for the degree of hypoglycaemia to be tested as several previous studies have demonstrated that this level of blood glucose is associated with significant impairment of cognitive functions [Deary, 1993b].

Although previous investigators have attempted to demonstrate attentional problems during acute hypoglycaemia using psychological tests, to our knowledge the present study is the first to confirm dysfunction of subdivisions of attention during hypoglycaemia using a test battery designed specifically to measure attention. The TEA was devised from the evidence on separable attention systems in the brain [Posner & Peterson, 1990]. Using the concept that attention is fractionated into different supramodal systems, it has been proposed that attention consists of at least three separate systems [Posner & Peterson, 1990]. A selection system is responsible for selecting relevant stimuli/processes and inhibiting irrelevant ones, a vigilance system maintains readiness to respond in the absence of external cues and an orientation system is responsible for engaging, moving and disengaging attention in space. The TEA attempts to measure aspects of the selection and vigilance systems and correlates significantly with existing measures of attention. For example, using factor analysis, the map search and telephone search load on the selective attention factor along with the Stroop Test and the Trail Making B test [Reitan & Davison, 1974].

In the present study, a significant deterioration was demonstrated during hypoglycaemia in tests of visual selective attention. These tests have shown an inability to ignore irrelevant information and to select specific targets from

complex visual arrays. Accuracy was preserved at the expense of speed in both the telephone search and visual elevator test (which assesses cognitive flexibility). This feature has been observed previously in studies of hypoglycaemia, and may indicate either that the speed of response is slower during hypoglycaemia or that individuals adopt a more cautious approach to avoid errors [Holmes et al, 1983, 1984]. However, it is important to note that in two previous studies by Holmes and her colleagues, verbal fluency and math recall were the variables from which this conclusion was derived [Holmes et al, 1983, 1984]. These are a measure of “crystallised ability”, i.e. abilities that are concerned with stored information and knowledge, and demonstrated that access to previously acquired information was not inaccessible during hypoglycaemia, but the rate of retrieval of this information was much slower. The present study demonstrates that this principle holds true for the acquisition of unfamiliar everyday tasks.

In the present study, the ability to manipulate information in auditory-verbal working memory deteriorated during hypoglycaemia as measured by the test of elevator counting with distraction. Using factor analysis, this test loads on the same factor as PASAT and Backward Digit Span tests, and may be sensitive to abilities such as complex mental arithmetic or mental computation of other problems [Robertson et al, 1994]. This test may also be sensitive to auditory selective attention although further research is required to confirm this possibility.

In the Elevator Counting with Reversal test, a significant order effect was apparent. This was an unexpected result because the relative complexity of this task was expected to be severely affected by moderate hypoglycaemia. Furthermore, no order effects were noted on this test during the standardisation and validation of the TEA [Robertson et al, 1994]. This order effect was most likely a type 1 statistical error and will need replication in future studies. Sustained attention using the lottery and elevator counting tasks was unaffected

by hypoglycaemia. These two subtests involve the ability to sustain attention to repetitive stimuli in the absence of external stimuli. This concords with a previous study where sustained attention to detail did not deteriorate with hypoglycaemia [Holmes et al, 1983], but is at variance with a more recent study where sustained attention to detail over a period of time was observed to be profoundly affected by hypoglycaemia [Draeos et al, 1995]. In the present study, significant ceiling effects for these tasks were observed with most subjects achieving the highest score possible during both study conditions. However, the task of conducting a telephone directory search while counting also involves a strong, sustained attention element, in that a counting task similar to the elevator counting must be done simultaneously with a visual search task. It is noticeable that the time per target score of this test increased significantly during hypoglycaemia. This test is analogous to assessing the ability to handle complex tasks that are a common requirement of everyday life – for example, writing a note from a telephone message while simultaneously speaking to the person giving the message. It is possible that these tests would have become impaired if the tasks had been of longer duration. The degree of impairment may also have been greater in other tests if the duration of testing had been prolonged. Following our study of attention during hypoglycemia, future studies should examine tests that are more demanding and of longer duration. Finally, it should be noted that the degree of attentional impairment found in this study might underestimate the real life scenario of hypoglycemia where the blood glucose may fall more rapidly from a higher starting point.

In the present study, fluid intelligence was not affected by hypoglycaemia. Various reasons may be proposed to explain this. The standard RPM were designed originally to cover the widest possible range of mental ability and to be applicable to persons of all age groups. As it was designed for children as well as adults, the first and second sets in the test, and the introductory problems in the third and fourth sets provide little more than training in the method of working. The test may, therefore, have been too elementary for most adult

subjects. However, the RPM were designed to provide a reliable estimate of a person's capacity to think clearly when allowed to work steadily at their own speed from the beginning to the end of a task without interruption. It covers the entire range of intellectual development from the time a child is able to grasp the idea of identifying a missing shape to complete a simple jigsaw or pattern, to the levels of ability required to form comparisons and reason by analogy. Although it is sufficiently short not to be unduly exhausting or unwieldy, there are an adequate number of difficult problems to discriminate between adults. However, in the present study, even when subjects were allowed to complete the test in their own time, no significant differences were observed in the scores achieved or the times taken to complete the task during both study conditions.

The hierarchical model of intelligence provides a parsimonious way to think about mental ability factors, and may also help explain our results. At the top of the hierarchy is general ability or *g* – a broad general factor that accounts for performance in a great variety of intellectual tasks. Tests that correlate highly with this factor are “complex” tests requiring abstract problem-solving analysis and rule inferring such as the RPM. Previous studies of hypoglycaemia looking at reading comprehension showed no deterioration in this complex cognitive skill [Holmes et al, 1983]. This suggests that higher level or associative cognitive skills may be less detectable or show no impairment during hypoglycaemia, in contrast to brain functioning that involves less complex informational analysis.

The RPM were administered towards the end of the hypoglycaemia session and it may be suggested that by this time the brains of the subjects had adapted to hypoglycaemia. This proposal is unlikely because the subjects were overtly neuroglycopenic before commencing the RPM test and also immediately afterwards, as demonstrated by their symptom scores. A previous study of non-diabetic subjects has demonstrated that hypoglycaemia of a similar degree and duration (60 minutes) was not associated with any evidence of cerebral



adaptation either in cognitive function or in symptom scores [Gold et al, 1995d]. In the present study, although no significant difference was demonstrated between the two study conditions, 50% of the subjects did show a deterioration in the RPM during hypoglycaemia. The present study had sufficient power to detect differences in cognitive function during acute hypoglycaemia compared to euglycaemia. Moreover, because subjects acted as their own controls the sample size provided approximately 94% power to detect a 0.5 standard deviation change (medium effect size) with a p value set at 0.05. It is possible that these differences would have become statistically significant with a larger cohort.

In summary, a deterioration in attention occurs during acute insulin-induced hypoglycaemia in non-diabetic humans, but fluid intelligence is preserved. Based on these results it can be surmised that many complex attention tasks relevant to everyday life are likely to be impaired during moderate hypoglycaemia. In the context of hypoglycaemia developing during everyday activities, examples of practical problems may include difficulty in filling out forms, looking up transport timetables, or finding items on supermarket shelves. The finding that accuracy was preserved at the expense of speed in tests of visual selective attention and attentional switching is of practical importance. Specifically, the tests of visual selective attention are pertinent to many of the activities that people encounter on a daily basis. It is reassuring that higher level constructs do not seem to become impaired during this acute metabolic insult. It is likely that people with type 1 diabetes, who are often exposed to hypoglycaemia, will be subject to a similar deterioration in attention, which could have important practical implications in everyday life. The results of a similar study in subjects with type 1 diabetes are described in Chapter 7.



## **CHAPTER 7**

### **STUDY 2**

#### **ACUTE HYPOGLYCAEMIA IN SUBJECTS WITH TYPE 1 DIABETES CAUSES ATTENTIONAL DYSFUNCTION WHILE NON-VERBAL INTELLIGENCE IS PRESERVED**

## 7.1 Introduction

As previously discussed, moderate hypoglycaemia occurs frequently in people with type 1 diabetes, and some mental functions deteriorate during this state [Deary et al, 1993b, Deary et al, 1999, Ryan et al, 1997]. The performance of tests that require attention, concentration, psychomotor skill, the accessing of longterm memory and the ability to ignore distracting information deteriorates when arterialised blood glucose falls below about 3.0 mmol/l [Hoffman et al, 1989, Widom & Simonson, 1990, Kerr et al, 1991b, Mitrakou et al, 1991, Wirsén et al, 1992]. Several studies have demonstrated a substantial degree of variability in individual responses to the effects of acute hypoglycaemia, and numerous moderators of cognitive function have been examined, including intelligence [Gold et al, 1995a], the presence or absence of diabetes [Herold et al, 1985, Heller et al, 1987, Widom & Simonson, 1990, Wirsén et al, 1992], and glycaemic control [Widom & Simonson, 1990, Ziegler et al, 1992]. However, few individual cognitive domains have received detailed examination. To fill this gap in our understanding, recent studies have attempted to address which specific aspects of these cognitive domains are disrupted by neuroglycopenia. They have also ascertained how abnormalities of cognitive function that are demonstrable by neuropsychological tests, are related to everyday mental tasks [McAulay et al, 2001, Sommerfield et al, 2003a, 2003b, Deary et al 2003, Warren et al, 2004].

Attention is a complex cognitive domain involving multiple subcomponent processes [Posner & Peterson, 1990, Pashler, 1998]. Because it comprises fundamental cognitive processes that are integral to many neuropsychological tests, it is difficult to examine attentional dysfunction in isolation. Standard neuropsychological tests purporting to assess attention deteriorate during controlled hypoglycaemia in non-diabetic adult humans [Mitrakou et al, 1991, Stevens et al, 1996], and in adults with type 1 diabetes [Widom & Simonson, 1990, Holmes et al, 1984, Pramming et al, 1986]. A previous study performed in Edinburgh, was the first to examine individual validated attentional processes

during hypoglycaemia in non-diabetic subjects, and demonstrated deterioration in attentional flexibility and speed of information processing, while sustained attention was preserved [McAulay et al, 2001].

Within the psychometric study of intelligence, general fluid intelligence reflects adaptive, problem-solving ability, and is largely non-verbal in nature. Raven's Progressive Matrices [Raven's Progressive Matrices, SPM, 1958] is a test of non-verbal reasoning that involves rule induction and application in abstract patterns. It is closely associated with general fluid intelligence [Marshalek et al, 1983]. General intelligence is a key finding and theoretical construct in the psychometric structure of human abilities [Carroll, 1993], and is an important influence on the quality of performance of many everyday activities [Gottfredson, 1997]. Although a deterioration in aspects of intelligence has been observed during acute hypoglycaemia both in non-diabetic subjects [Stevens et al, 1989, McCrimmon et al, 1996], and in people with diabetes [Holmes et al, 1983, Kerr et al, 1991b, Ewing et al, 1998], to our knowledge few studies of non-diabetic or diabetic adults have included subtests that were designed specifically to measure aspects of non-verbal intelligence [McAulay et al, 2001, Warren et al, 2004].

It is not known whether the results of the previous study in non-diabetic subjects can be applied to subjects with type 1 diabetes. Thus, the aim of the present study was to examine the effects of acute, controlled, insulin-induced hypoglycaemia on attention and on general non-verbal intelligence in adults with type 1 diabetes, and to establish whether any variation exists with those observed in non-diabetic subjects.

## 7.2 Subjects and Methods

### *Subjects*

Sixteen adults with type 1 diabetes were recruited from the diabetes outpatient clinics at the Royal Infirmary of Edinburgh to participate in the present study. The median (range) age was 25.5 (18-39) years and duration of diabetes was 8.0 (2.5-15) years with a mean (SD) Body Mass Index of 24.1 (1.8) kg/m<sup>2</sup>. The mean (SD) National Adult Reading Test (NART) number correct score was 27 (7.8). Thus, the group comprised people whose mean was just above average intelligence, with an overall predicted full scale intelligence quotient of around 109. Their mean (SD) HbA1c, measured by high-performance liquid chromatography (Variant II Hemoglobin Testing System; Biorad Diagnostics, Hercules, CA) was 7.7 (1.0)% (local DCCT-aligned, non-diabetic reference range: 4.3-6.5%). None of the participants had a history of chronic disease, hypertension, previous head injury, seizure or blackouts, alcohol or drug abuse, or psychiatric disorder. None had any intercurrent illness, nor was taking medication (other than insulin and the combined oral contraceptive pill) and none of the subjects had any evidence of microvascular disease. The absence of retinopathy was confirmed by direct ophthalmoscopy and digital retinal imaging. Peripheral neuropathy was excluded by clinical examination, and none of the participants had microalbuminuria. No subjects had a history of impaired awareness of hypoglycaemia. Care was taken to avoid hypoglycaemia in the 48 hours prior to the cognitive testing, with regular blood glucose monitoring, including bedtime measurements on the night before each study. The study was deferred for one week if there was evidence at that time of biochemical hypoglycaemia (blood glucose <4.0 mmol/l). Ethical permission for the study was given by the Lothian Medical Ethical Advisory Committee, and all subjects gave their written informed consent.

### *Study Design*

The subjects were studied on two occasions, separated by at least one week. The experiment had a repeated measures, counterbalanced design, i.e. half of the subjects underwent the euglycaemia session first, followed by the hypoglycaemia study, and the other half were studied in the reverse order. A modified hyperinsulinaemic glucose clamp technique [DeFronzo et al, 1979] was used to adjust the blood glucose to a predetermined level. In one condition, hypoglycaemia was induced (blood glucose 2.6 mmol/l) and maintained at this level, and in the other condition the blood glucose concentration was maintained at 4.5 mmol/l (euglycaemia). During the two study conditions (euglycaemia and hypoglycaemia) tests of cognitive function were administered and the subjects completed a questionnaire on the symptoms of hypoglycaemia. Subjects were blinded as to the order of the studies and to their prevailing blood glucose concentration at all times throughout the procedure.

### *Procedure*

Each session commenced at 0800 hrs after an overnight fast, and the subjects omitted their morning dose of insulin. The procedure was as detailed in section 5.1.4.

### *Cognitive Function Tests*

The Test of Everyday Attention (TEA) [Robertson et al, 1994] and the Raven's Standard Progressive Matrices (RPM) [Raven's Progressive Matrices, SPM, 1958] were used to measure attention and intelligence respectively. The order of the tests was identical during each study condition.

### **Test of Everyday Attention (TEA)**

The TEA was devised from the evidence on separable attention systems in the brain [Posner and Peterson, 1990]. Using the concept that attention is fractionated into different supramodal systems, it has been proposed that attention consists of at least three separate systems [Posner & Peterson, 1990].



A selection system is responsible for selecting relevant stimuli/processes and inhibiting irrelevant ones, a vigilance system maintains readiness to respond in the absence of external cues and an orientation system is responsible for engaging, moving and disengaging attention in space. The Test of Everyday Attention attempts to measure aspects of the selection and vigilance systems and correlates significantly with existing measures of attention. The TEA is described in detail in section 5.2.2.

Briefly, the TEA is divided into eight subtests and has parallel forms. Subjects were asked to pretend that they were on holiday in Philadelphia in the USA, and were told that they would be asked to perform various tasks such as looking for symbols on maps, consulting telephone directories, attending to lottery numbers, and going up and down in elevators. The attention processes examined and their corresponding test(s) are shown in table 7.1.

#### **Raven's Progressive Matrices (RPM)**

The RPM examine general non-verbal intelligence and specifically measure the inductive ability to find and apply rules that make it easier to bring order to complex situations and events [Carpenter et al, 2000]. The RPM are considered to be the single best measure of general fluid intelligence [Marshalek et al, 1983]. The Matrices' items are diagrammatical puzzles exhibiting serial change in two dimensions simultaneously. Each puzzle has a part missing which the subject has to find among the answer options provided. The correct answer is found by discovering and correctly applying the rules governing the changes in each item's pattern. The test consists of 60 items divided into five sets, each consisting of 12 items. Subjects were assigned two scores for this test; the number correct at 20 minutes and the number correct at completion (no time limit). By doing this, the speed of accurate intellectual work and the total capacity for orderly thinking of the subjects could be assessed.

**Table 7.1** The subtests and attention processes of the TEA

Attentional Process	Test
Selective Attention	Map Search
Speed Of Information Processing	Telephone Search
Attentional Switching	Visual Elevator
Sustained Attention	Lottery Counting Elevator Counting Telephone Search While Counting
Divided Attention	Telephone Search While Counting
Attentional Switching	Elevator Counting With Reversal Elevator Counting With Distraction

### *Symptoms of hypoglycaemia*

A subjective self-rating system (The Edinburgh Hypoglycemia Scale) [Deary et al, 1993a] was applied at four time points: baseline, before and after the TEA, and after the RPM. The symptoms of hypoglycaemia were classified as autonomic (palpitations, sweating, shaking and hunger), neuroglycopenic (drowsiness, confusion, inability to concentrate, speech difficulty and blurred vision) and non-specific (headache and nausea). Each symptom was graded on a Likert scale of 1 to 7 (1 = not present, 7 = very intense). The total for each subgroup of hypoglycaemic symptoms was calculated. A validated 7-point scale was used to assess impaired awareness of hypoglycaemia [Gold et al, 1994].

### *Statistical analysis*

The results were analysed independently for each subtest of the TEA and the RPM. A general linear model (repeated measures analysis of variance) was used with order of session as a ‘between-subjects’ factor with two levels (euglycaemia-hypoglycaemia or hypoglycaemia–euglycaemia), and condition as a ‘within-subjects’ factor with two levels (euglycaemia versus hypoglycaemia). A similar model was used to analyse the symptoms of hypoglycaemia, with the

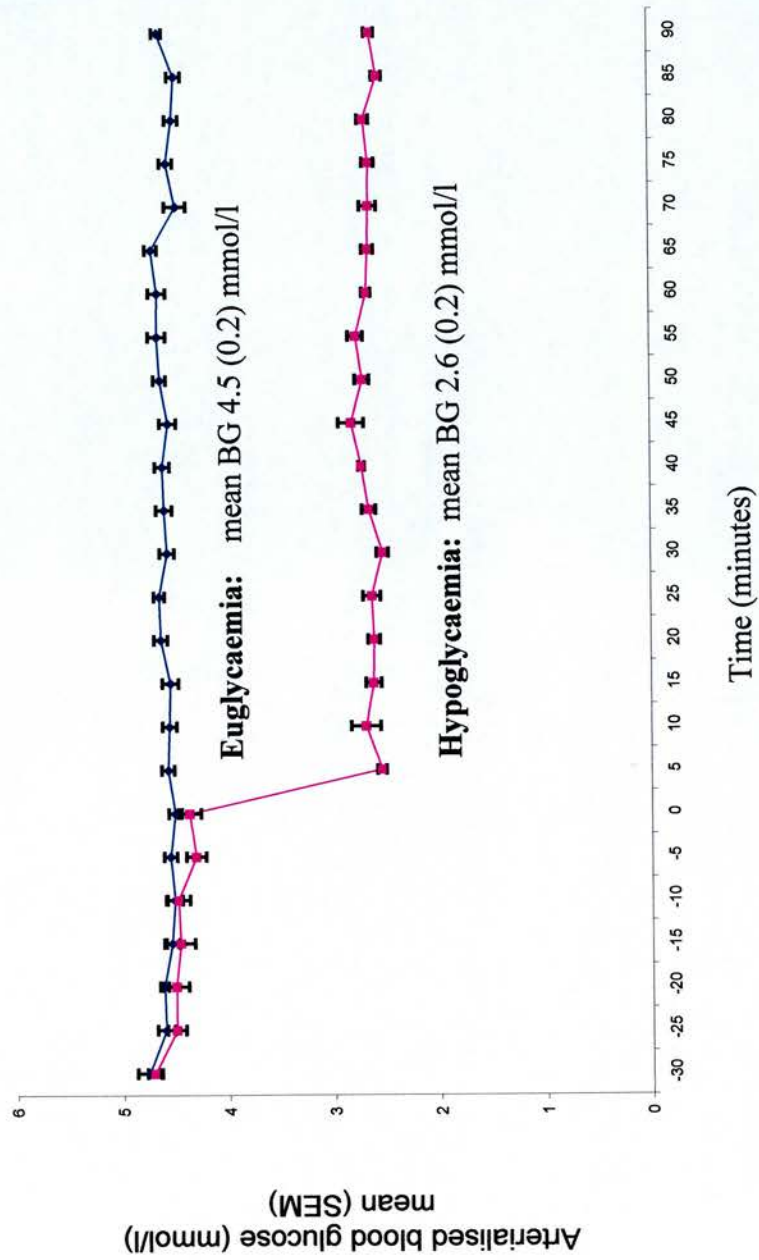
addition of time as a 'within-subjects' factor with four levels. During the symptoms analysis, the principal outcome statistic was any (experimental versus time) interaction as this indicated the effects of hypoglycaemia on symptoms controlled for day-to-day variation by including baseline scores. A p value of less than 0.05 was considered to be significant. Effect size was calculated using Eta squared ( $\eta^2$ ).  $\eta^2$  is the proportion of the variance in the test scores accounted for by study condition (euglycaemia versus hypoglycaemia). A  $\eta^2$  score of 0.25-0.5 was considered a moderate effect size [Cohen, 1992]. All analyses were performed using SPSS version 11.0 for Windows.

### **7.3 Results**

A stable blood glucose plateau was achieved during each condition (figure 7.1). The mean (SD) blood glucose concentration during the hypoglycaemia clamp was 2.6 (0.2) mmol/l, and during euglycaemia was 4.5 (0.2) mmol/l. The initial statistical analysis revealed that no significant order effects had occurred.

#### *Symptoms*

During the hypoglycaemia study arm, autonomic symptom scores increased from a mean (SD) of 5.1 (1.2) at baseline to 7.9 (2.8) during hypoglycaemia ( $p=0.005$ ). The neuroglycopenic symptom score increased from a mean (SD) of 6.0 (1.9) at baseline to 11.1 (5.4) during hypoglycaemia ( $p=0.01$ ). No significant increment was observed in the general malaise symptom scores, which increased from 2.1 (0.3) at baseline to 3.3 (1.8) during hypoglycaemia ( $p=0.04$ ). There were no significant changes in symptom scores during the euglycaemia study arm. The symptom reports confirmed that all subjects had intact symptomatic awareness of hypoglycaemia at the predetermined low blood glucose concentration and, more pertinently, that symptomatic neuroglycopenia had developed.



**Figure 7.1** Blood glucose profiles during hypoglycaemia and euglycaemia in 16 subjects with type 1 diabetes. Values are shown as mean (standard error of the mean)

### *Tests of Attention*

The results of the attention tests are summarised in tables 7.2 and 7.3.

#### *Visual Selective Attention*

Acute hypoglycemia caused a significant deterioration in tests sensitive to a visual selective attention deficit. The mean number of map symbols circled was lower during hypoglycaemia at both one minute ( $p=0.032$ ,  $\eta^2=0.29$ ) and at two minutes ( $p=0.042$ ,  $\eta^2=0.26$ ). By contrast, in the telephone search task, no difference was demonstrated between euglycaemia and hypoglycaemia in the number of symbols located ( $p=0.46$ ). However, the mean time taken to complete the task increased significantly during hypoglycaemia ( $p=0.022$ ,  $\eta^2=0.32$ ). The results demonstrate that a visual selective attention decrement had developed during hypoglycaemia.

#### *Auditory Selective Attention/Auditory Verbal Working Memory*

With the auditory elevator test with distraction, the achieved score declined during hypoglycaemia with a large effect size ( $p=0.001$ ,  $\eta^2=0.59$ ) (figure 7.2). Furthermore, the score attained on the elevator test with reversal deteriorated during hypoglycaemia ( $p=0.013$ ,  $\eta^2=0.39$ ).

#### *Sustained Attention*

Sustained attention did not deteriorate during hypoglycaemia using either the lottery ticket test ( $p=0.26$ ) or the elevator counting test ( $p=0.15$ ).

#### *Attentional Switching*

In the visual elevator task, no difference was observed in the raw score between the two study conditions ( $p=0.21$ ). However, a significantly longer time was required to complete the visual elevator task during hypoglycaemia with a large effect size ( $p<0.0001$ ,  $\eta^2=0.78$ ).



### *Divided attention*

In the task that involved search of a telephone directory while counting, no significant difference was observed in the number of symbols that were located during either study condition ( $p=0.67$ ). However, the time taken to complete the task was higher during hypoglycaemia ( $p=0.001$ ,  $\eta^2=0.58$ ). The time per target score, which is the ratio of the number of circled symbols divided by the time taken for the task, was higher during hypoglycaemia with a moderate effect size ( $p=0.036$ ,  $\eta^2=0.28$ ). The dual task decrement was not significantly different between the two conditions ( $p=0.95$ ).

### *Non-verbal intelligence*

Using Raven's Progressive Matrices, no significant differences were observed between euglycaemia and hypoglycaemia in the scores achieved either at 20 minutes or upon completion of the test. The mean (SD) RPM score at 20 minutes was 50.1 (5.6) during euglycaemia and 49.0 (6.4) in the hypoglycaemia condition ( $p=0.24$ ,  $\eta^2=0.12$ ). Upon completion, the mean (SD) score was 51.7 (6.1) in the euglycaemia condition and 50.6 (6.0) during hypoglycaemia ( $p=0.11$ ,  $\eta^2=0.22$ ) (figure 7.3). No significant differences were found between the two study conditions in the times taken to complete the test.

**Table 7.2** Selective attention during euglycaemia and hypoglycaemia in 16 subjects with type 1 diabetes.  
 Reproduced from McAulay et al 2006a with permission of Blackwell Science Ltd.  
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<i>Attentional system</i>	<i>Subtest</i>	<i>Euglycaemia</i>	<i>Hypoglycaemia</i>	<i>p value</i>	$\eta^2$	$\dagger \eta^2$ for non-diabetics
<b>Visual selective attention</b>	Map search symbols in one minute	50.0 (8.8)	42.6 (10.0)	0.032	0.29	0.32
	Map symbols circled in two minutes	74.1 (4.0)	70.3 (7.7)	0.042	0.26	0.12
	Telephone search time (secs)	47.4 (6.0)	52.5 (8.0)	0.022	0.32	0.36
	Telephone search correct symbols	18.5 (2.7)	18.7 (2.0)	0.46	0.04	0.001
	Telephone search raw score (time/target)	2.6 (0.6)	2.9 (0.7)	0.003	0.48	0.36
<b>Auditory selective attention</b>	Elevator counting with distraction	8.9 (1.3)	7.3 (2.0)	0.001	0.59	0.40
	Elevator counting with reversal	8.0 (1.7)	7.1 (1.8)	0.013	0.39	0.01

Values are mean (SD)

$\eta^2$  is the proportion of the variance in the test scores accounted for by study condition (euglycaemia vs hypoglycaemia)

$\dagger$  Data from McAulay et al (2001)

**Table 7.3** Attentional function during euglycaemia and hypoglycaemia in 16 subjects with type 1 diabetes.  
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<i>Attentional system</i>	<i>Subtest</i>	<i>Euglycaemia</i>	<i>Hypoglycaemia</i>	<i>p value</i>	<i>η<sup>2</sup></i>	<i>†η<sup>2</sup> for non-diabetics</i>
<b>Attentional switching</b>	Visual elevator raw score	9.3 (0.9)	8.8 (1.4)	0.21	0.11	0.03
	Visual elevator timing score (secs/switch)	3.0 (0.6)	3.4 (0.9)	0.04	0.26	0.69
	Visual elevator time (secs)	120.0 (20.5)	150.0 (23.4)	< 0.0001	0.78	0.76
<b>Sustained attention</b>	Elevator counting	6.9 (0.3)	6.7 (0.6)	0.15	0.14	0.03
	Lottery tickets	9.6 (0.7)	9.2 (0.9)	0.26	0.09	0.08
<b>Divided attention</b>	TSWC time (secs)	49.1 (7.7)	55.2 (10.3)	0.001	0.58	0.13
	TSWC correct symbols	18.4 (1.6)	18.7 (1.6)	0.67	0.01	0.07
	TSWC time /target score	2.7 (0.5)	3.0 (0.7)	0.036	0.28	0.26
	Dual task decrement	0.4 (0.7)	0.4 (0.6)	0.95	0.00	0.01

Values are mean (SD)  
 η<sup>2</sup> is the proportion of the variance in the test scores accounted for by study condition (euglycaemia vs hypoglycaemia)  
 TSWC – Telephone Search While Counting, † Data from McAulay et al (2001)

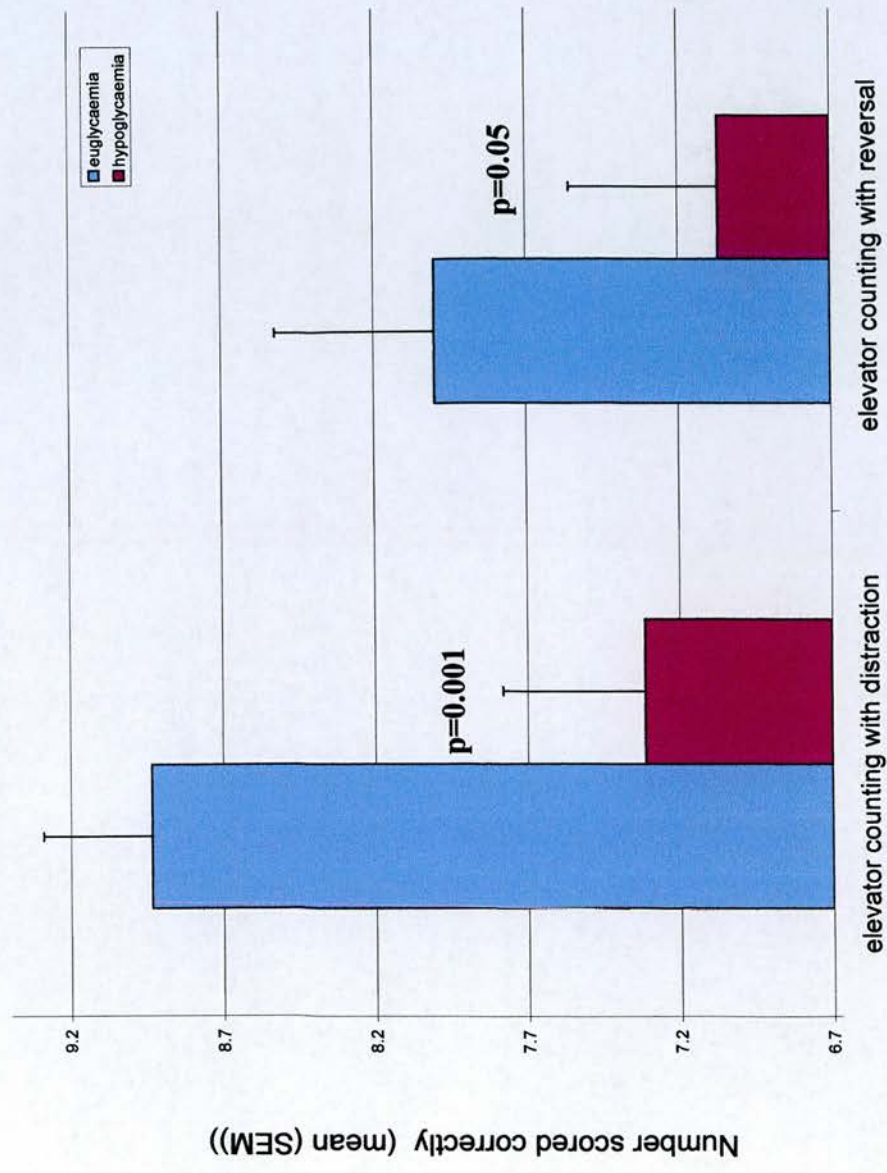
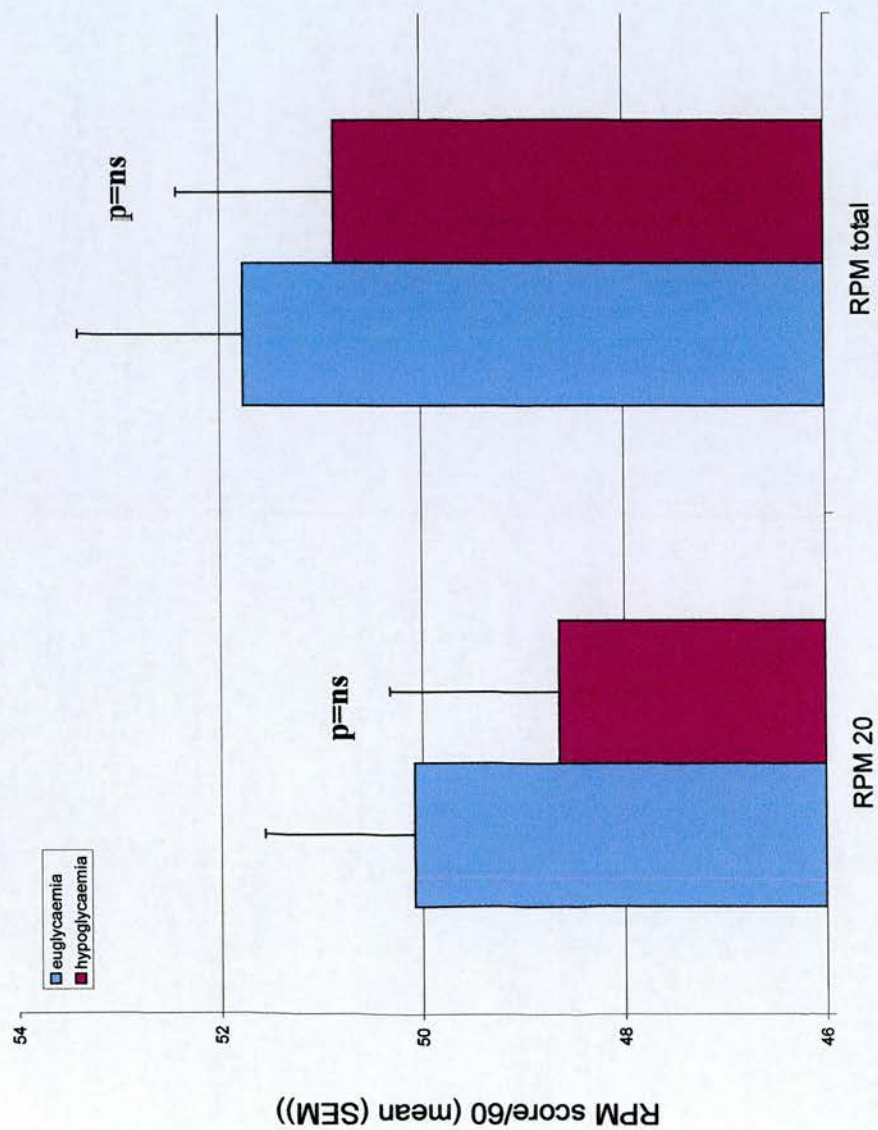


Figure 7.2

Auditory selective attention during hypoglycaemia. Data derived from McAulay et al, 2006



**Figure 7.3** Fluid intelligence in 16 subjects with type 1 diabetes. Data from McAulay et al 2006



## 7.4 Discussion

In the present study, impairment of function in the subdivisions of attention was demonstrated to occur during hypoglycaemia in adults with type 1 diabetes. A cognitive test battery was employed that was designed specifically to measure multiple facets of attention. Visual selective attention deteriorated during hypoglycaemia with a moderate effect size, whereas auditory selective attention was exquisitely sensitive to hypoglycaemia with a large effect size. Mean scores on the test of divided attention were significantly poorer during hypoglycaemia. By contrast, no significant effect was evident on sustained attention or nonverbal intelligence. The subjects had good glycaemic control and had no evidence of microvascular disease or co-morbidities that might influence cognitive performance.

A previous study in Edinburgh which used an identical study design and cognitive function tests, examined the effects of acute hypoglycaemia in non-diabetic adults of similar age and observed a broadly similar distribution of cognitive dysfunction during hypoglycaemia [McAulay et al, 2001]. In that study, a decline in the rate of information processing was demonstrable in visual and auditory selective attention and in attentional switching. Although the data from both of these studies are congruent with the received wisdom that acute hypoglycaemia slows the speed of processing, the TEA measures other cognitive processes. Furthermore, important differences between these two studies provide further insights on whether diabetes is a factor that moderates an individual's susceptibility to cognitive dysfunction during hypoglycaemia [Herold et al, 1985, Widom & Simonson, 1990, Wirsén et al, 1992].

In the present study, significant decrements occurred during hypoglycaemia in the test scores for auditory selective attention (figure 2 and table 2). Unlike the other subtests in the TEA, these are not timed, so the decrements noted are not accounted for by slowing of speeded processing. These two subtests measure the ability to manipulate and sequence information in auditory-verbal working

memory [Robertson et al, 1994]. Using principal components analysis, they share the same factor structure as the Paced Auditory Serial Addition Test (PASAT) and Backward Digit Span tests [Robertson et al, 1994]. In the study of non-diabetic volunteers, who were of a similar age (mean (SD) 28.7 (5.3) years) and premorbid IQ (mean (SD) correct for NART 28.9 (5.8)) as the subjects with diabetes in the present study (see results), acute hypoglycaemia led to a deterioration in the elevator counting with distraction test, but not elevator counting with reversal [McAulay et al, 2001]. Indeed, the effect size during hypoglycaemia was smaller ( $\eta^2=0.40$ ) for elevator counting with distraction in non-diabetic volunteers, compared with the present study of subjects with diabetes ( $\eta^2=0.59$ ), suggesting a greater cognitive decline in subjects with diabetes (table 7.2). An example of a clinical correlate for these tests of auditory verbal working memory is the ability to work out complex mental arithmetic, an activity that is used by most people on a daily basis.

Important differences in visual selective attention deficits during hypoglycaemia were also observed. Although hypoglycaemia led to a similar reduction in the number of map search symbols found in one minute during both studies, only the subjects with diabetes showed a significant deterioration in the score for the number of map symbols circled at two minutes (table 2). While the map search subtest is a timed test, and to an extent will measure speed of processing, it also evaluates the ability to select target stimuli, while ignoring powerfully competing distractors, and hence also involves a considerable degree of selective attention. Supporting evidence for this can be found using principal components analysis, in which the map search shares the factor structure of visual selective attention, in common with tests such as Trails B [Reitan, 1958] and the d2 visual search task [Brickenkamp, 1962]. Therefore, because the effects of the other tests of speeded processing administered during hypoglycaemia were similar both in the non-diabetic and diabetic subjects, it is possible that acute hypoglycaemia has a greater impact on visual selective attention in subjects with type 1 diabetes, especially when the test is prolonged.

This argument is supported by a further study where acute hypoglycaemia caused a significant and marked deterioration in visual information processing [McCrimmon et al, 1996]. An alternative explanation is that the cognitive 'reserve' for speeded tests, or visual selection tests, is diminished in people with type 1 diabetes.

In the present study, sustained attention, as assessed by the lottery and elevator counting tasks, was not impaired during hypoglycaemia. This is consistent with a previous study of non-diabetic subjects [McAulay et al, 2001], and since most subjects achieved the highest score possible during both study conditions, suggests that significant ceiling effects had occurred. These results are at variance with a different study in which sustained attention to detail was profoundly affected by hypoglycaemia [Draeos et al, 1995]. However, in that study the digit vigilance test [Lewis & Rennick, 1979] was used as a measure of sustained attention. In this test, subjects are given a page containing rows of digits and instructed to cancel target digits (either the number 6 or 9). The number of targets located in 2 minutes as well as the percentage of targets erroneously missed are scored, providing measures of speed and accuracy. It is highly likely that this test is measuring speeded processing, and this may account for the significant deterioration in this subtest in the study by Draeos et al [1995]. In the present study, although it is possible that a test of longer duration may have increased the sensitivity of detecting a deterioration, it appears that sustained attention to detail over a short period of time (10 minutes) is unaffected by hypoglycaemia. Finally, the degree of attentional impairment observed in the present study may underestimate the severity of the effect when it is experienced during a "real life" episode of hypoglycaemia when the rate of fall of blood glucose may be more rapid.

In the present study, non-verbal intelligence did not diminish significantly during hypoglycaemia, as was observed in a previous study of non-diabetic volunteers [McAulay et al, 2001] (figure 3). This outcome was unexpected

because so many aspects of cognition are adversely affected during hypoglycaemia [Deary et al, 1999]. Furthermore, the RPM is known to have a substantial correlation with working memory [Ackerman et al, 2002], which is very sensitive to hypoglycaemia [Deary et al, 2003, Sommerfield et al, 2003b]. It is conceivable that the cognitive abilities required for activities such as those tested by the RPM are resistant to the effects of hypoglycaemia, but this hypothesis contravenes the received wisdom that complex tasks are more susceptible than simple tasks to disruption during acute hypoglycaemia [Deary et al, 1999]. It is unlikely that the brain would have adapted to cope with the effects of hypoglycaemia during a study of this relatively short duration [Gold et al, 1995d].

A more likely explanation is that the standard matrices that were used here were too easy for this particular group of adults. These matrices were designed originally to cover the widest possible range of mental ability and to be applicable to persons of all ability levels. At the beginning of each set in the RPM most of the problems are simple. This hypothesis about the difficulty level of the standard RPM was tested in non-diabetic adults by using a more difficult test of general fluid intelligence, the Raven's Advanced Progressive Matrices (RAPM) [Warren et al, 2004]. In that study, acute hypoglycaemia caused a significant deterioration in the RAPM, suggesting that a ceiling effect had occurred using the standard RPM. However, it is relevant that in the study by Warren et al [2004] the mean number correct score of the subjects, using the National Adult Reading Test, was higher (at 40) compared to the present study of people with type 1 diabetes and to the previous study of non-diabetic subjects [McAulay et al, 2001] in both of which it was 28. People with a higher intelligence may be more susceptible to cognitive dysfunction during hypoglycaemia [Gold et al, 1995a], which may explain, in part, the observations of the study by Warren et al [2004]. In addition, the RAPM provides a means of examining high-level inductive reasoning ability, spreading the distribution of scores in the top 25% of the population and assessing more accurately a person's



speed of intellectual work; timed tests such as the RAPM discriminate against those who work more slowly and carefully. When the diabetic subjects in the present study were allowed to complete the test in their own time, no significant differences were observed in the scores achieved, or the times taken, to complete the task during both study conditions, which is consistent to observed responses in the previous study of non-diabetic adults [McAulay et al, 2001].

The present study has demonstrated that acute controlled hypoglycaemia causes attentional dysfunction in adults with type 1 diabetes, while there was a non-significant decline in non-verbal reasoning. The tests of attention that were used in the present study are plausible, realistic and relevant to everyday activities, thus tasks utilising complex intellectual activity that are relevant to everyday life activities, such as procedures at work or the process of driving a car, are likely to be impaired during the moderate insulin-induced hypoglycaemia that is experienced frequently by people with insulin-treated diabetes. The severity of the attentional deficit during acute moderate hypoglycaemia was dependent upon which attentional system was being examined. The degree of hypoglycaemia examined in this study is common in people with type 1 diabetes, and does not affect conscious level, so a similar deterioration during hypoglycemia is likely to have important practical implications for many tasks in the everyday lives of people with type 1 diabetes. The differential deterioration observed in subtests of visual selective attention and auditory verbal working memory in subjects with type 1 diabetes compared to non-diabetic subjects, raises a potentially contentious issue and implies that a diagnosis of diabetes may act as a susceptibility factor to cognitive disruption during hypoglycaemia.



## **CHAPTER 8**

### **STUDY 3**

#### **IMPACT OF ACUTE HYPOGLYCAEMIA ON MOOD, MOTIVATION, THINKING CONTENT AND THINKING STYLE IN SUBJECTS WITH TYPE 1 DIABETES**

## 8.1 Introduction

Insulin is an essential hormone for normal metabolism and cell function, and is required to drive glucose into cells. Since the human brain is almost totally dependent on the oxidation of glucose supplied by the circulation for its energy requirements, a reduction of blood glucose supply will usually result in impairment of cognitive function. In healthy people, physiological mechanisms, including the release of counterregulatory hormones to promote a return to normal blood glucose, have evolved that are designed to protect the brain against hypoglycaemia and, therefore, this is a rare event. However, people with type 1 diabetes, who need to inject subcutaneous insulin to control blood glucose, frequently experience blood glucose levels low enough to result in cognitive disruption [Deary, 1993b], and more rarely seizures [MacLeod et al, 1993], and even coma [Hart & Frier, 1998].

The development of the hyperinsulinaemic glucose clamp technique [DeFronzo et al, 1979] has enabled the effects of hypoglycaemia in humans to be studied under steady-state conditions. It allows investigators to 'clamp' the blood glucose at a predetermined level for a prolonged period, allowing detailed examination of the physiological and cognitive changes that occur during hypoglycaemia. Over the last two decades, a considerable body of research has accumulated on the effects of acute hypoglycaemia on brain function. This has been done in various ways; in addition to administering tests of cognitive function [Holmes et al, 1983, 1984, Hoffman et al, 1989, Widom & Simonson, 1990, Kerr et al, 1991a, Mitrakou et al, 1991, Wirsén et al, 1992, Cox et al, 1993b, Pramming et al, 1986], some have examined the neuroglycopenic symptoms generated during hypoglycaemia [Hepburn et al, 1991]. At an even more basic level, others have applied electrophysiological measures such as brain-evoked potentials [Amiel et al, 1991] and functional brain imaging [Rosenthal et al, 2001]. It has been shown that cerebral blood flow increases globally during hypoglycaemia, and that the pattern of regional cerebral blood flow alters during hypoglycaemia in people with diabetes, with increases to the

superior frontal regions and right thalamus, and decreases to the right posterior cingulate cortex and putamen [MacLeod et al, 1994].

Controlled studies of hypoglycaemia have demonstrated that a wide range of mental functions deteriorate when the arterialised blood glucose concentration declines below 3.0 mmol/l. Abnormalities occur in several domains, including verbal function, attention and concentration, memory, executive and motor function [Deary et al, 1993b, Deary et al, 1999, Ryan et al, 1997]. Furthermore, a hierarchy exists in the sensitivity of different aspects of cognition, with complex tasks being more severely impaired than simpler cognitive tasks [Hoffman et al, 1989, Widom & Simonson, 1990, Kerr et al, 1991b, Mitrakou et al, 1991, Wirsén et al, 1992, Cox et al, 1993b, Pramming et al, 1986]. Until recently, few individual cognitive domains had received detailed examination. However, studies are now attempting to address which particular aspects of these domains are disrupted by neuroglycopenia, and how the abnormalities of cognitive function that are demonstrable by neuropsychological tests, relate to everyday mental tasks. For example, the aspects of memory and attention that are most affected by hypoglycaemia have recently been described [McAulay et al, 2001, McAulay et al, 2006, Sommerfield et al, 2003a, 2003b, Deary et al 2003, Warren et al, 2004].

Although many aspects of cognitive function have been examined during acute hypoglycaemia, other important areas have been neglected. Performance challenges, such as attaining proficiency in the workplace and passing examinations, have high importance for people in Westernised societies, so that comprehension of the nature of subjective experience in these settings is of both theoretical and practical relevance. In particular, little information is available concerning the subjective feelings that are generated by acute hypoglycaemia. Much of psychology is shaped by a 'trilogy of mind', dividing psychological functioning into the three domains of affect (mood), conation (motivation) and cognition [Hilgard, 1980]. Demanding tasks readily elicit a variety of 'stress'

responses that impinge on these domains, such as fatigue, anxiety, worry and loss of motivation (Hockey, 1997). According to cognitive theories of stress, how a person appraises and then copes with a given situation may drive individual differences both in subjective stress responses and in objective behaviour [Matthews & Wells, 1996]. Thus, substantial disturbance of subjective state may provide at least an indirect marker for potential behavioural impairments. Participants undergoing laboratory experiments, such as a hyperinsulinaemic glucose clamp, probably have concerns about whether they will cope adequately with task requirements.

Few studies have examined the non-cognitive changes in cerebral function that occur during acute hypoglycaemia including the influence on emotions (affect, mood). The emotional consequences of living with the ever-present risk of hypoglycaemia can affect the personal lives of both the individual with diabetes and other members of the family. Therefore, it is not surprising that most individuals with recurrent exposure to severe hypoglycaemia develop an aversion to it. In general, hypoglycaemia promotes expression of negative mood states including diminished energetic arousal, decreased happiness, increased anxiety and increased anger [Gold et al, 1995c, Hepburn et al, 1995, McCrimmon et al, 1999a, 1999b]. However, to our knowledge, no studies have examined either the role of motivation on the performance and outcomes of controlled studies of hypoglycaemia, or the perception of workload during the tasks administered. The conative aspect of mind has not been explored during hypoglycaemia. Furthermore, the subjective component of subjects' style of thinking and beliefs, such as self-esteem, concentration, and control and confidence, in relation to the tasks that they are asked to perform during hypoglycaemia has not been examined (i.e. subjective cognition). The subjective factors that may index potential interference with cognitive task performance have also been neglected.

The present study examined the three aspects of mental function during acute, controlled, insulin-induced hypoglycaemia. Thus, mood, motivation and cognition were examined in adults with type 1 diabetes using a validated measure, the Dundee Stress State Questionnaire (DSSQ) [Matthews et al, 1999]. Workload was also assessed.

## **8.2 Materials and Methods**

### *Subjects*

Sixteen adults with type 1 diabetes were recruited from the diabetes outpatient clinics at the Royal Infirmary of Edinburgh. Their clinical characteristics are shown in table 8.1. The median (range) age was 25.5 (18-39) years and the duration of diabetes was 8.0 (2.5-15) years with a mean (SD) Body Mass Index of 24.1 (1.8) kg/m<sup>2</sup>. The mean (SD) National Adult Reading Test (NART) number correct score was 27 (7.8). Thus, the group comprised people whose mean was above average intelligence, with an overall predicted full scale intelligence quotient of around 109. Their mean (SD) HbA1c, measured by high-performance liquid chromatography (Variant II Hemoglobin Testing System; Biorad Diagnostics, Hercules, CA) was 7.7 (1.0)% (local Diabetes Control and Complications Trial-aligned, non-diabetic reference range: 4.3-6.5%). None of the participants had a history of chronic disease, hypertension, previous head injury, seizure, blackout, alcohol or drug abuse, or psychiatric disorder. None had any intercurrent illness, nor was taking any medication (other than insulin or the combined oral contraceptive pill), and none of the subjects had any evidence of microvascular disease. The absence of retinopathy was confirmed by direct ophthalmoscopy and digital retinal imaging. Peripheral neuropathy was excluded by clinical examination, and none of the participants had microalbuminuria. No subjects had a history of impaired awareness of hypoglycaemia. Care was taken to avoid hypoglycaemia in the 48 hours prior to the cognitive testing, by performing frequent blood glucose monitoring, including bedtime measurements on the night before each study. The study was deferred for one week if there was evidence at that time of biochemical



hypoglycaemia (blood glucose < 4.0 mmol/l). Ethical permission for the study was given by the Lothian Medical Ethical Advisory Committee, and all subjects gave their written informed consent.

**Table 8.1** Clinical characteristics of sample

Age (years)	25 (18-39)
Male (%)	62.5
Duration of diabetes (years)	8.0 (2.5-15)
BMI (kg/m <sup>2</sup> )	24.1 (1.8) #
HbA1c (%)	7.7 (1.0) #
Data are median (range), unless otherwise indicated # mean (SD)	

### *Study Design*

The subjects were studied on two occasions, separated by at least one week. The experiment had a repeated measures, counterbalanced design, i.e. half of the subjects underwent the euglycaemia condition first, followed by the hypoglycaemia condition, and the other half were studied in the reverse order. A modified hyperinsulinaemic glucose clamp technique [DeFronzo et al, 1979] was used to adjust the blood glucose to a predetermined level. In one condition, hypoglycaemia was induced (blood glucose 2.6 mmol/l) and maintained at this level, and in the other condition the blood glucose concentration was maintained at 4.5 mmol/l (euglycaemia). During these two study conditions (hypoglycaemia and euglycaemia, respectively) tests of cognitive function were administered and the subjects completed a questionnaire on the symptoms of hypoglycaemia. The cognitive tests that were administered were the Test of Everyday Attention (TEA) [Robertson et al, 1994] and the Raven's Progressive Matrices (RPM) [Raven's Progressive Matrices, SPM, 1958]. The DSSQ was administered before, and after, the cognitive function tests during both arms of the study. Subjects were unaware of the order in which the studies were performed and were not informed about their prevailing blood glucose concentration at all times throughout the procedure.

### *Procedure*

Each session commenced at 0800 hrs after an overnight fast, and the subjects omitted their morning dose of insulin. The procedure was as detailed in section 5.1.4.

### *The Dundee Stress State Questionnaire*

The DSSQ has been described in detail in section 5.2.4. In the present study, Annexe A was administered prior to the TEA and RPM, and Annexe B was completed after these tests. Briefly, the TEA [Robertson et al, 1994] is a validated batch of attention tests that measure aspects of the selection and vigilance systems of attention (section 5.2.2), and the RPM [Raven's Progressive Matrices, SPM, 1958] examine general non-verbal intelligence (section 5.2.3). These two tests were administered over approximately 90 minutes. Instructions for the DSSQ emphasise rating immediate rather than typical subjective experience, to ensure reporting of short-term states rather than enduring traits (i.e. personality dispositions that show much greater temporal stability [Matthews et al, 2003]. The scales show adequate internal consistencies with Matthews et al (2002) reporting Cronbach alpha coefficients ranging from 0.77-0.89. The DSSQ has been validated as a state index in studies showing that it is sensitive to external stress factors, appropriately correlated with cognitive stress factors, and predictive of objective performance indices [Matthews et al, 1999, 2001, 2002].

### **Test of Everyday Attention (TEA)**

The TEA was devised from the evidence on separable attention systems in the brain [Robertson et al, 1994]; it attempts to measure aspects of the selection and vigilance systems. Briefly, the TEA is divided into eight subtests and has parallel forms (table 5.1). Subjects were asked to pretend that they were visiting Philadelphia in the USA, and were told that they would be asked to perform various tasks such as looking for symbols on maps, consulting telephone directories, and travelling in an elevator. The results of the TEA and RPM used

in this study have been reported elsewhere [McAulay et al, 2006]. Briefly, visual selective attention deteriorated during hypoglycaemia with a moderate effect size ( $p=0.03$ ), whereas auditory selective attention was exquisitely sensitive to hypoglycaemia with a large effect size ( $p=0.001$ ). Mean scores on the test of divided attention were poorer during hypoglycaemia ( $p=0.001$ ), whereas no significant effect was evident on sustained attention ( $p=0.15$ ) or nonverbal reasoning ( $p=0.24$ ) [McAulay et al, 2006].

### *Symptoms of hypoglycaemia*

A validated self-rating system for subjective symptoms of hypoglycaemia (The Edinburgh Hypoglycemia Scale) [Deary et al, 1993a] was applied at four time points: baseline, before and after the TEA, and after the RPM. The symptoms of hypoglycaemia were classified as autonomic (palpitations, sweating, shaking and hunger), neuroglycopenic (confusion, drowsiness, inability to concentrate, speech difficulty and blurred vision) and non-specific (nausea and headache). Each symptom was graded on a Likert scale of 1 to 7 (1 = not present, 7 = very intense). The total for each subgroup of hypoglycaemic symptoms was calculated.

### *Statistical analysis*

The results were analysed independently for each subtest of the DSSQ. A general linear model (repeated measures analysis of variance) was used, with order of glycaemic condition as a 'between-subjects' factor with two levels (euglycaemia-hypoglycaemia or hypoglycaemia-euglycaemia). There were two 'within-subjects' factors, each with two levels; experimental condition (euglycaemia versus hypoglycaemia) and time (baseline versus experimental). A similar model was used to analyse the symptoms of hypoglycaemia; however time was a 'within-subjects' factor with four levels. During the symptoms analysis, the principal outcome statistic was any (experimental versus time) interaction as this indicated the effects of hypoglycaemia on symptoms controlled for day-to-day variation by including baseline scores. A  $p$  value of

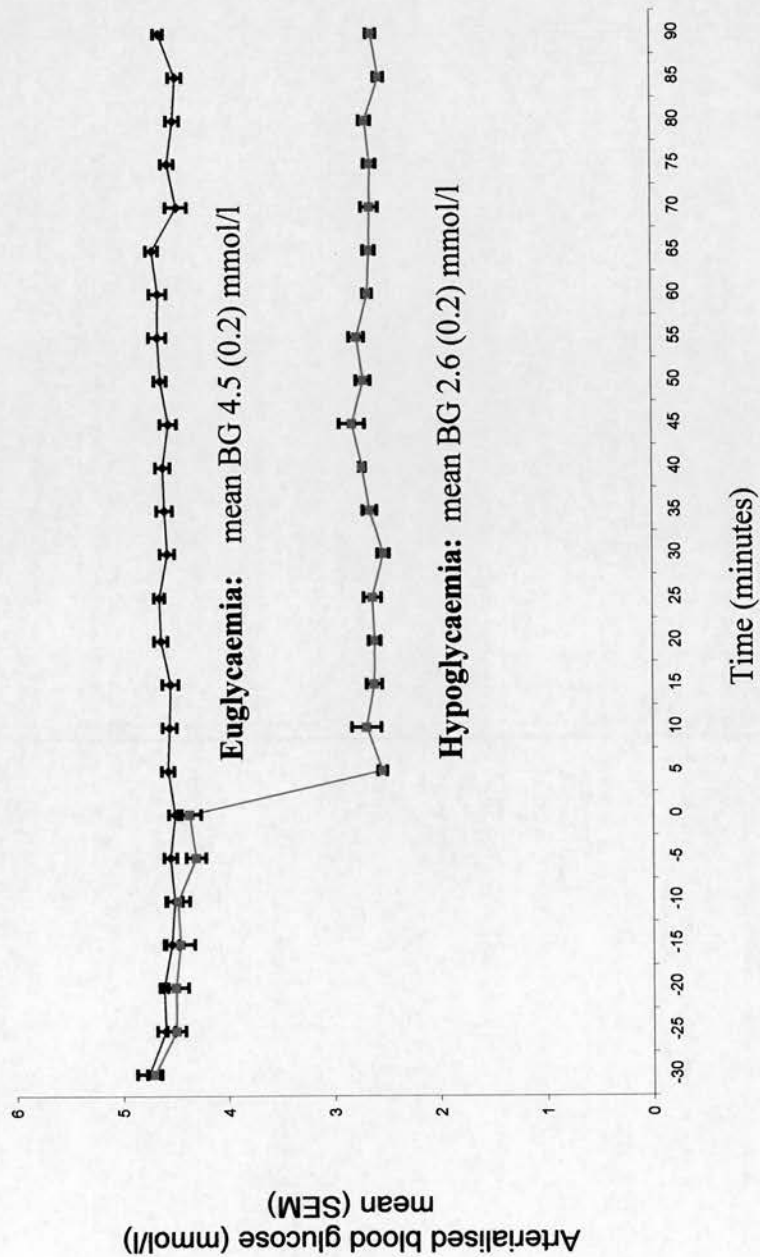
less than 0.05 was considered to be significant. Effect size was calculated using Eta squared ( $\eta^2$ ).  $\eta^2$  is the proportion of the variance in the test scores accounted for by the relevant study effect. A  $\eta^2$  score of 0.25-0.5 is considered a moderate effect size [Cohen, 1992]. All analyses were performed using SPSS version 11.0 for Windows.

### **8.3 Results**

A stable blood glucose plateau was achieved during each condition (figure 8.1). The mean (SD) blood glucose concentration during the hypoglycaemia clamp was 2.6 (0.2) mmol/l, and during euglycaemia was 4.5 (0.2) mmol/l. The initial statistical analysis revealed that no significant order effects had occurred.

#### *Symptoms*

During the hypoglycaemia study arm, significant increments occurred in the scores for autonomic ( $p=0.005$ ) and neuroglycopenic symptoms ( $p=0.01$ ), but no significant change was observed in the symptoms of general malaise ( $p=0.4$ ). There were no significant changes in symptom scores during the euglycaemia study arm. The symptom reports confirmed that all subjects had intact symptomatic awareness of hypoglycaemia at the predetermined low blood glucose concentration and, more pertinently, that symptomatic neuroglycopenia had developed.



**Figure 8.1** Blood glucose profiles during hypoglycaemia and euglycaemia in 16 subjects with type 1 diabetes. Values are shown as mean (standard error of the mean)



### *DSSQ results*

The results are summarised in tables 8.2 and 8.3.

#### *Mood*

Acute hypoglycaemia caused a significant increase in anxiety with a concomitant reduction in energy levels. The mean score for energetic arousal decreased significantly during hypoglycaemia ( $p=0.03$ ,  $\eta^2=0.48$ ) with a moderate effect size. A significant increase occurred in scores for tense arousal during hypoglycaemia ( $p=0.05$ ,  $\eta^2=0.25$ ). No significant changes were observed in the scores for hedonic tone ( $p=0.11$ ) during hypoglycaemia, and a trend to higher anger/frustration scores ( $p=0.09$ ,  $\eta^2=0.19$ ) was noted. No significant differences were noted before and after cognitive testing, and the time by condition interaction was not significant for any mood scale.

#### *Motivation and workload*

A trend towards reduced motivation was observed during the hypoglycaemia arm of the study ( $p=0.07$ ,  $\eta^2=0.21$ ). During both arms, a significant decrease occurred in motivation over the period of cognitive function testing, with a moderate to large effect size ( $p=0.01$ ,  $\eta^2=0.35$ ). Subjects reported less motivation afterwards. Perception of workload was higher during hypoglycaemia, but did not achieve statistical significance ( $p=0.11$ ,  $\eta^2=0.17$ ).

#### *Thinking style*

A significant time by study condition interaction for self-focus was observed, with a moderately large effect size ( $p=0.02$ ,  $\eta^2=0.32$ ). Inspection of the mean values in table 8.3 reveals that, although self-focus is similar at baseline during hypoglycaemia and euglycaemia, the subjects' mean levels of self-focus were very high when reported at post-test. That is, their reports indicate that self-focus was especially high during hypoglycaemia. The main effect of hypoglycaemia did not result in a significant change in self-focus ( $p=0.14$ ) or self-esteem ( $p=0.44$ ). Similarly, no significant pre- and post-task changes on

self-esteem ( $p=0.15$ ) or self-focus ( $p=0.65$ ) were demonstrable during each arm of the study. Concentration, and control and confidence did not alter significantly during hypoglycaemia ( $p=0.14$  and  $p=0.19$  respectively). Similarly, no significant pre-and post-task changes developed in concentration ( $p=0.22$ ) or control and confidence ( $p=0.10$ ). There were no further time by condition interactions.

#### *Thinking content*

Significant main effects of acute hypoglycaemia were observed both in task-relevant and -irrelevant interference. Task-relevant interference decreased during hypoglycaemia ( $p=0.03$ ,  $\eta^2=0.29$ ). By contrast, for task-irrelevant interference, a large increment in scores was observed during hypoglycaemia ( $p=0.02$ ,  $\eta^2=0.32$ ). No main effects of time and no significant time by condition interactions were found.

**Table 8.2** Mood and conation during euglycaemia and hypoglycaemia in 16 subjects with type 1 diabetes

	Euglycaemia		Hypoglycaemia		Euglycaemia vs hypoglycaemia		Before vs after		Euglycaemia vs hypoglycaemia vs before/after	
	Pretest	Posttest	Pretest	Posttest	P value	$\eta^2$	P value	$\eta^2$	P value	$\eta^2$
<b>Mood</b>										
Energetic arousal	23.7±4.75 (14-31)	23.2±5.42 (13-30)	18.7±5.41 (11-28)	18.50±4.72 (11-26)	0.03	0.48	0.72	0.01	0.91	0.01
Tense arousal	13.19±5.23 (8-28)	13.06±4.15 (8-21)	15.87±5.88 (8-31)	16.44±5.98 (8-26)	0.05	0.25	0.87	0.002	0.72	0.01
Hedonic tone	28.44±3.05 (22-32)	28.44±3.55 (20-32)	27.81±3.04 (20-32)	26.06±4.09 (16-32)	0.11	0.17	0.24	0.10	0.10	0.18
Anger/frustration	6.12±2.68 (5-15)	6.06±1.48 (5-10)	6.94±2.14 (5-12)	7.56±3.05 (5-14)	0.09	0.19	0.55	0.02	0.30	0.08
<b>Conation</b>										
Motivation	52.94±9.34 (33-65)	49.31±10.76 (24-62)	50.12±7.47 (38-62)	46.00±12.89 (18-63)	0.07	0.21	0.01	0.35	0.88	0.01
Workload	--	23.38±9.90 (6-40)	--	26.44±11.83 (4-30)	0.12	0.17	--	--	--	--

Values are mean±SD (range)  
 $\eta^2$  is the standardised difference between the two means and is the proportion of the variance in the test scores accounted for by study condition  
(euglycaemia vs hypoglycaemia ± vs time)

**Table 8.3** Subjective cognition during euglycaemia and hypoglycaemia in 16 subjects with type 1 diabetes

	Euglycaemia		Hypoglycaemia		Euglycaemia vs hypoglycaemia		Before vs after		Euglycaemia vs hypoglycaemia vs before/after	
	Pretest	Posttest	Pretest	Posttest	P value	$\eta^2$	P value	$\eta^2$	P value	$\eta^2$
<b>Cognition</b>										
Self-focus	6.87±4.47 (1-15)	4.81±3.60 (0-12)	6.87±4.82 (1-21)	8.37±6.15 (0-24)	0.14	0.15	0.65	0.01	0.02	0.32
Self-esteem	23.12±5.45 (10-28)	22.37±5.11 (11-28)	22.19±4.41 (14-28)	21.94±4.90 12-28)	0.44	0.43	0.15	0.03	0.60	0.02
Concentration	24.12±4.3 (14-28)	22.25±6.19 (11-27)	22.25±6.27 (10-28)	21.00±5.85 (6-29)	0.14	0.15	0.22	0.10	0.73	0.01
Control and confidence	16.19±4.21 (6-21)	15.06±5.77 (4-24)	15.8±15.29 (8-24)	13.25±6.78 (2-24)	0.19	0.17	0.10	0.18	0.41	0.05
Task relevant interference	16.62±5.23 (10-28)	16.62±5.23 (8-31)	14.75±4.78 (9-26)	16.19±6.51 (8-28)	0.03	0.29	0.44	0.04	0.14	0.15
Task irrelevant interference	11.19±3.51 (8-20)	10.43±2.78 (8-18)	12.94±3.13 (8-18)	11.94±3.73 (8-18)	0.02	0.32	0.21	0.11	0.84	0.01

Values are mean±SD (range)

$\eta^2$  is the standardised difference between the two means and is the proportion of the variance in the test scores accounted for by study condition (euglycaemia vs hypoglycaemia ± vs time)

## 8.4 Discussion

To our knowledge this study is the first to examine comprehensively the subjective cognitive and conative aspects of mental function during controlled hypoglycaemia. This complements previous research which demonstrates the disruptive effects of hypoglycaemia on cognitive and emotional mental states [Deary, 1999]. Prior to completing cognitive tests, hypoglycaemia and euglycaemia did not differ with respect to reported self-focus of attention. However, when subjects reported on their mental state during task performance, self-focus of attention was much higher during hypoglycaemia. Self-focus of attention refers to a state of self-preoccupation and reflection, or private self-consciousness. During the hypoglycaemia condition as a whole, task-relevant interference decreased whereas task-irrelevant interference increased, i.e. there was an increase in thoughts that were irrelevant to the cognitive tasks performed. We replicated previous findings that a less energetic and more tense mood develops during hypoglycaemia [Gold et al, 1995c, Hepburn et al, 1995, McCrimmon et al, 1999a, 1999b]. Thus, viewed as a 'stressor', hypoglycaemia conforms to the typical finding that stressors produce patterned changes in multiple psychological state indices, rather than some global change in stress or anxiety [Hockey, 1997, Matthews et al, 2002]. That is to say, some elements of state are more sensitive to hypoglycaemia than others.

The features of the multifaceted state changes associated with hypoglycaemia will now be addressed in more detail, and their potential impact on behaviour and performance is assessed. These new findings about how cognition is affected during hypoglycaemia provide information about the effect of a low blood glucose on the brain. The subjects have extra thoughts, irrelevant to the task, in their minds, even before performance of the tasks. This might be caused by an awareness of cognitive impairment during hypoglycaemia. However, such extra content in consciousness is likely to drain processing resources and limit performance in its own right. Extensive evidence from studies of evaluative anxiety has demonstrated detrimental effects of cognitive interference



on information processing and performance [Zeidner, 1998]. Thus, performance of the hypoglycaemic person is doubly compromised in that the mood changes of reduced energy and (to a lesser degree) increased tension are also associated with impairments on demanding attentional tasks [Matthews et al, 2001].

These effects of hypoglycaemia were main effects, and appeared during both pre- and post-test, indicating a general state difference. In addition, the time by study condition interaction for self-focus indicated an effect in which hypoglycaemia moderated the subjective response to performing the tasks. Interestingly, the increase in self-focused attention appeared in awareness after the participants had performed a cognitive task, suggesting that the challenge of this cognitive effort and engagement elicited additional self-referent processing that might also impair mental performance. The state change seen in hypoglycaemia is unusual, in that self-focused attention typically declines during task performance, as subjects orient attention away from the self and towards the task [Matthews et al, 2002]. Previous research suggests that the combination of self-focused attention and high tension or anxiety is often detrimental to performance [Carver, 1996, Wells & Matthews, 1994]. In summary, it would appear that the brain is not only less cognitively competent and more dysphoric during hypoglycaemia, it is also more self-aware and distracted when required to perform effortful processing. More time is occupied by thinking about the task, the self, and other things, possibly leaving fewer processing resources for successful completion of the cognitive tasks, whether in the laboratory or during everyday life. It could be argued that the effects of acute hypoglycaemia on self-focus represent a type 1 error. Of course, this is a possibility, and in such a new area of study these results will require replication in future studies.

The tests of cognitive function utilised during studies of hypoglycaemia have been criticised as being imperfect because of the perceived practice effect that may take place, i.e. repetition of the test will improve performance. The

resulting improvement results from practice and will diminish the impairment caused by hypoglycaemia, leading to the incorrect conclusion that cognitive function is unaffected or only modestly impaired. Furthermore, fatigue may increase the sensitivity of cognitive tests, in that those tests attempted at the end of a test period may be more sensitive to the effects of hypoglycaemia [Heller & Macdonald, 1996]. It may also be difficult to discriminate the effects of affect, or mood, from those of its cognitive and motivational concomitants (although the multidimensional assessment provided by the DSSQ may allow such discriminations to be made). For example, the effects of anxiety on behaviour might be mediated by affect (e.g. tension) or by cognitions (e.g. intrusive thoughts and worries), or by motivations, such as the urge to withdraw from the threatening situation. Another variable is that the motivation to perform a task may decline over the cognitive function testing period and between test days, thereby influencing the results. Effort reduction is a common response to tasks that have little perceived value [Hockey, 1997]. Vigilance tasks are often lower in workload but require the performer to cope with the monotony of the task [Scerbo, 1998]. Thus reduced motivation, energy and concentration may all be expressions of the fatigue control mode.

In this context, two broad modes have been suggested. In an 'overload' mode, the person maintains effort to compensate for processing inefficiency, generating emotional strain, loss of performance on low-priority tasks components, and provoking physiological responses such as catecholamine secretion. With the 'fatigue' mode, the person reduces the target level of performance, so that less effort is required, and the person primarily experiences loss of motivation and energy rather than strain [Hockey, 1997]. In the present study, motivation declined to a similar extent during both the euglycaemia and hypoglycaemia arms of the glucose clamp, thus reassuring and supporting the results and conclusions of previous studies of hypoglycaemia. Although workload scores did increase during hypoglycaemia, they did not achieve statistical significance, suggesting that despite moderate hypoglycaemia, the

neuroglycopenia induced may conceal the workload of the task being undertaken.

Within the affective domain, mood states provide a background context for psychological functioning, and impinge on different functions such as attention, judgement, and memory [Matthews, 1992]. In the present study, hypoglycaemia produced a negative mood state with a significant fall in energy levels and a concomitant rise in anxiety levels. These findings concur with previous observations in Edinburgh [Hepburn et al, 1995] in a study utilising an insulin infusion to induce hypoglycaemia in 12 subjects without diabetes and 15 subjects with type 1 diabetes. They are also broadly similar to the results of another study, in which a hyperinsulinaemic glucose clamp was used to induce hypoglycaemia in 24 non-diabetic adults [Gold et al 1995c]. In that study, hypoglycaemia induced significant increments in the scores for tense arousal with a decrement in that for energetic arousal. Furthermore, in another study of healthy adult volunteers [McCrimmon et al 1999a], which also used the hyperinsulinaemic glucose clamp technique, a rise in anxiety levels was demonstrated during hypoglycaemia. However, in these previous studies of non-diabetic subjects [Gold et al, 1995c, McCrimmon et al, 1999a], subjects became less happy (hedonic tone) during hypoglycaemia in contrast to the present findings. This is perhaps not surprising since non-diabetic volunteers are unaccustomed to hypoglycaemia, whereas this state is experienced on a frequent basis by people with type 1 diabetes. Finally, the small rise in anger scores during hypoglycaemia in the present study is consistent with previous data [McCrimmon et al, 1999b] and is compatible with the symptom of aggression, or even frustration, that is occasionally manifest as an expression of hypoglycaemia in some individuals.

Despite the wide-ranging effects of acute hypoglycaemia on the various subcomponents of attention [McAulay et al, 2001, McAulay et al, 2006], in the present study, the subjects' perception of their concentration abilities was

unaffected during prolonged moderate hypoglycaemia. Similar results were observed for control and confidence, with no decline in the scores for these tasks during hypoglycaemia. These data are congruent and extend that found in ambulant subjects with type 1 diabetes who were asked to evaluate their decision to drive based on their perception of what their blood glucose concentration was at that time [Clarke et al, 1999]. In that study, approximately half of subjects decided that it was safe to drive at least 50% of the time when their blood glucose level was less than 3.9 mmol/l. However, self-focus of attention did increase significantly between euglycaemia and hypoglycaemia signifying an increase in sensitivity to criticism from others, implying that significant worry occurs during hypoglycaemia in addition to the elevated level of anxiety demonstrated earlier.

A high level of interference may be generated by many different specific thoughts about personal concerns [Carver, 1996, Sarason et al, 1986]. The state is defined by the overall level of intrusive thoughts, not by the specific contents of the thoughts. Acute hypoglycaemia increased task-irrelevant interference demonstrating that the state of hypoglycaemia is characterised by intrusive thoughts which are unconnected to the task that is currently being undertaken. It is also possible that this state may persist across a change of context. For example, worries experienced during an episode of acute hypoglycaemia may transfer to state at the workplace or at home, thus affecting quality of life.

Although we controlled for the recognised moderators of cognitive dysfunction during hypoglycemia such as glycaemic control, antecedent hypoglycemia, age, pre-morbid intelligence and impaired awareness of hypoglycemia, there were important individual differences between subjects in this study. The mechanism underlying this phenomenon remains elusive but there may be a potential association with serum angiotensin-converting enzyme (s-ACE) activity. The frequency of severe hypoglycemia varies greatly between people with diabetes, and is positively correlated with s-ACE activity [Pedersen-Bjorgaard U et al,



2001, Pedersen-Bjorgaard U et al, 2003, Nordfeldt et al, 2003]. Low s-ACE activity confers greater ability to function during physical stress [Montgomery et al, 1998, Gayagay et al, 1998], and people with diabetes with low s-ACE activity may be better able to maintain cognitive function during acute hypoglycemia. However, the mechanism through which such an effect might be mediated is unknown.

The present study has demonstrated that the motivation to perform the tasks of the TEA and RPM becomes impaired during acute controlled hypoglycemia. Therefore, it is reasonable to assume that with an appropriate study design (counter-balanced design and euglycemia control arm) and suitable methodology (appropriate tests to reduce practice effects for cognitive tests), the effects of workload, fatigue and motivation are unlikely to be modifying the results of studies of hypoglycemia. Acute hypoglycemia induces a state of significant worry and anxiety which is likely to have an impact on our patients' social, personal and work activities. It is disconcerting that during hypoglycemia, subjects with type 1 diabetes seem to be relatively unconcerned about their potential danger and predicament, and continue to feel in control of, and confident about their abilities. This has obvious implications for performing tasks at work and for driving skills.



**Part IV**  
**Clinical Study**

## **CHAPTER 9**

### **STUDY 4**

#### **OPTIMAL TIME OF ADMINISTRATION OF INSULIN LISPRO IN THE SETTING OF A HIGH FAT MEAL**

## 9.1 Introduction

The advent of fast-acting analogues of human insulin (insulin lispro and insulin aspart) which are more rapidly absorbed following subcutaneous injection, and have a faster onset and shorter duration of action than human soluble insulin [Howey et al, 1994], has allowed greater flexibility in their time of administration. Although they are usually injected immediately before meals to avoid inducing preprandial hypoglycaemia [Anderson et al, 1997, Garg et al, 1996], a delayed rise in postprandial blood glucose or a reduced magnitude of the glycaemic response to food may increase the risk of early postprandial hypoglycaemia.

The rate of gastric emptying is an important determinant of the temporal response of postprandial blood glucose [Horowitz et al, 1993], and is influenced by the composition of a meal [Kong et al, 1996, Macdonald, 1996]. Liquids leave the stomach more rapidly than solids [Kelly, 1980, Collins et al, 1991, Lyrenas et al, 1997], and gastric emptying is slower when the composition of a meal is high in fat [Hunt et al, 1968, Houghton et al, 1990, Sidery et al, 1994]. Studies using insulin lispro have shown that administration a few minutes before a meal is the optimal time of injection in most clinical situations. However, in people with type 1 diabetes the absorption of nutrients is slower when a meal is high in fat (particularly in the solid-phase) because gastric emptying is slower [Horowitz et al, 1991]. In this situation, postprandial administration of insulin lispro may be necessary to provide a closer match between the time action profile of the fast-acting insulin and the postprandial rise in blood glucose, and so reduce the risk of postprandial hypoglycaemia [Burge et al, 1997a, Scherthaner et al, 1998, Strachan & Frier, 1998]. These previous studies used test meals characterised by their composition of carbohydrate and fat, and some had a relatively high liquid content [Burge et al, 1997b, Strachan & Frier, 1998]. While these test meals were chosen to investigate particular aspects of the composition of food in relation to insulin action, most were absorbed more

rapidly than the usual high fat, solid-phase meals that are typical of the average Western diet.

The aim of the present study was to examine the effect of either pre- or post-prandial administration of insulin lispro on the pharmacodynamics of blood glucose following the consumption of a high fat, solid-phase meal, which is popular in the UK and is often consumed by many people with type 1 diabetes. The principal objective was to determine which time of administration of insulin was less likely to allow the development of early post-prandial hypoglycaemia.

## **9.2 Research design and methods**

### *Subjects*

Twelve subjects with Type 1 (insulin-dependent) diabetes were recruited from the diabetes outpatient clinic of the Royal Infirmary of Edinburgh. All had type 1 diabetes, diagnosed according to World Health Organization criteria, for more than two years and had a HbA1c concentration below 9.3% [non-diabetic range 4.3-6.5%]. All subjects were using insulin lispro [Eli Lilly & Co., Basingstoke, UK] as part of a basal bolus regimen (all subjects administered isophane insulin once daily at bedtime). No subjects were overweight or had significant microvascular complications of diabetes (other than background retinopathy) or other medical disorders, and none had a history of dyspepsia or gastric fullness after meals. Autonomic neural function was assessed using standard tests of cardiovascular reflexes [Ewing & Clarke, 1985] and none had evidence of autonomic dysfunction. Table 9.1 shows the clinical characteristics of the subjects with type 1 diabetes. The study was approved by the local medical ethics advisory committee, and all subjects gave written informed consent before taking part.

**Table 9.1** Clinical characteristics of 12 subjects with type 1 diabetes

<b>Group characteristic</b>	<b>Median (range)</b>
Gender (M/F)	6/6 <sup>#</sup>
Age (years)	31 (19-49)
Duration of diabetes (years)	10 (2-13)
BMI (kg/m <sup>2</sup> )	25.5 (22-29)
HbA <sub>1c</sub> (%)	8.2 (7-9.3)
Total daily insulin dose (units/kg)	0.71 (0.41-1)

<sup>#</sup> ratio

The subjects attended on three separate occasions separated by at least one week. Lunchtime was chosen for the time of the test meal as this was considered to provide the most stable pre-meal blood glucose concentration, which was less likely to be affected by fasting hyperglycaemia or asymptomatic nocturnal hypoglycaemia, and fluctuations in glycaemic control affecting blood glucose later in the day. The test meal consisted of a pre-weighed portion of fried fish and french fried (chipped) potatoes (170 gms fish, 85 gms fried potatoes). The fish was coated in batter (a mixture of flour, eggs and milk, used to coat certain foods before frying) and with the chipped potatoes was deep-fried in cooking oil. This was freshly prepared in a local commercial outlet. An allowance of 150 ml of water was administered with each test meal. At the first visit, subjects attended for a preliminary assessment of the insulin dose that would be required for the test meal. The subjects estimated, from their previous experience, the dose of pre-prandial insulin lispro that they would require to achieve satisfactory control of blood glucose for the study meal. The estimated dose of insulin lispro was self-administered subcutaneously using an injection site on the anterior abdominal wall, five minutes before ingestion of the study meal. The insulin dose used for the subsequent study days was determined on the basis of these preliminary results in which the target capillary blood glucose concentration was to be between 7 and 10 mmol/l 5 hours after ingestion of the meal. The same dose of insulin lispro was used in the two subsequent studies.



The insulin regimen for each subject remained unchanged throughout the study period.

On the two study days, the subject injected the pre-determined dose of insulin lispro either 5 minutes before (time zero minus five minutes) the test meal (started at time zero), or 20 minutes after the meal had been commenced. The order of the time of administration was randomised and the pre-determined insulin dose and the abdominal site of injection of insulin remained constant for both studies. To assess the glucodynamic response, serial venous blood samples for glucose estimation were obtained, via an in-dwelling cannula before the meal and at 30-minute intervals for a period of five hours. The study was discontinued immediately if at any time venous blood glucose concentrations fell to less than 2.5 mmol/l, or if symptoms of hypoglycaemia developed with a venous blood glucose below 3.0 mmol/l.

On each study day, the pre-meal glucose concentration was required to be within the range of 4.0-12.0 mmol/l. A capillary blood glucose value that was outside this range required the study to be rescheduled on another day. This was necessary to ensure that the blood glucose concentrations for individuals at the commencement of each study were comparable on both study days as the prevailing level of glycaemia is known to influence the rate of gastric emptying; hyperglycaemia delays gastric emptying [MacGregor et al, 1976, Fraser et al, 1990, Oster-Jorgensen et al, 1990], while hypoglycaemia accelerates gastric emptying [Schvarcz et al, 1993].

#### *Assay methods*

Whole venous blood glucose was determined using the glucose oxidase method (Yellow Springs Instruments 2300 stat). Glycated haemoglobin (HbA1c) was determined using high speed liquid chromatography based on an ion-exchange reverse-partition method (Variant II Hemoglobin Testing System; Biorad

Diagnostics, Hercules, CA) (local DCCT-aligned non-diabetic reference range: 4.3-6.5%).

### *Statistical analyses*

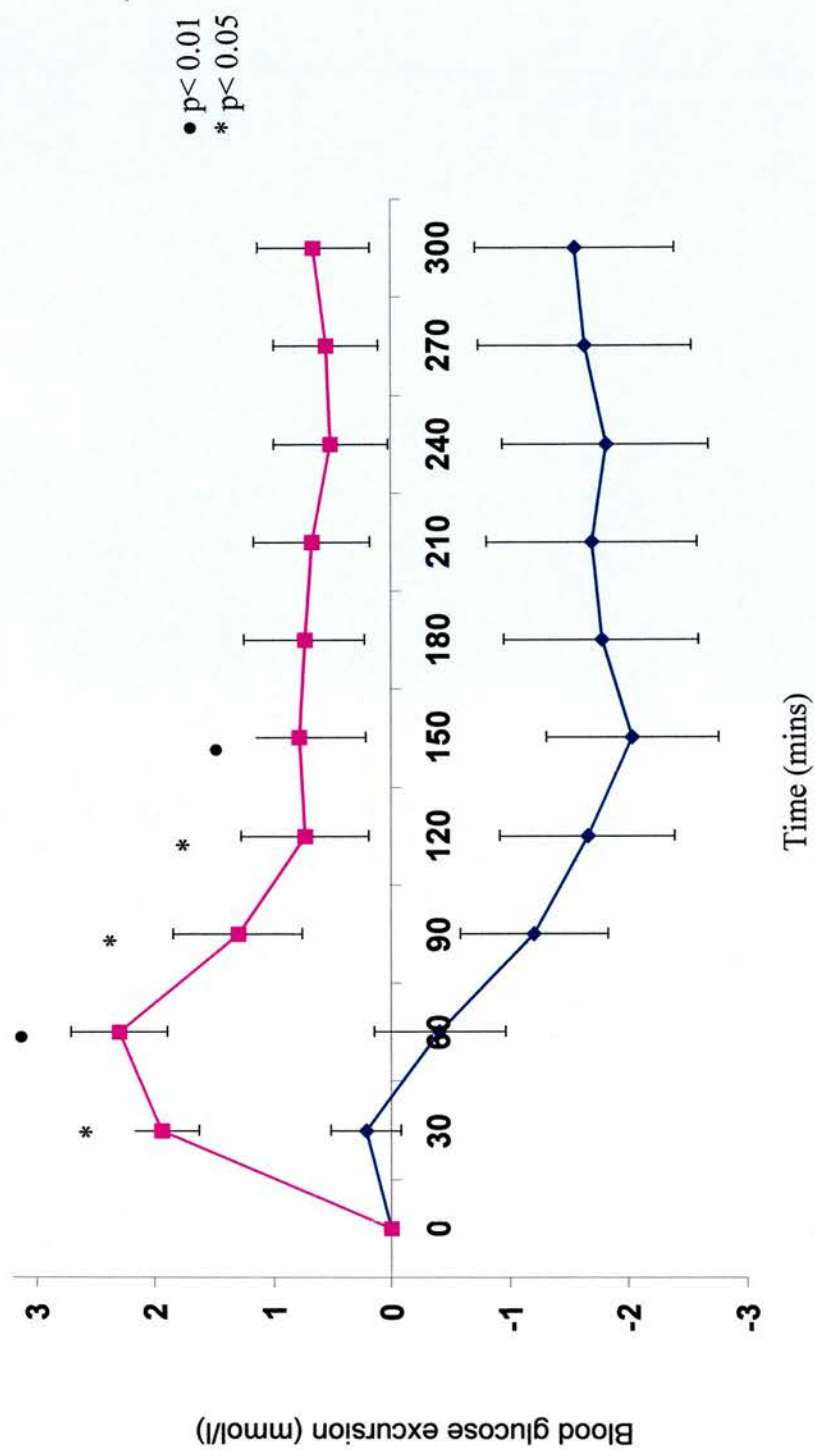
Baseline blood glucose concentrations were compared using Student's t test for paired data. Postprandial blood glucose excursions were compared using a repeated measures analysis of variance (ANOVA). Post hoc analyses were performed using Student's t test for paired data. A p value of less than 0.05 was considered significant for the ANOVA; a p value less than 0.01 was considered significant for the paired t test analyses, to reduce the risk of a type 1 statistical error occurring in view of the multiple analyses that were performed. All analyses were performed using SPSS version 10.0 for Windows.

## **9.3 Results**

The baseline fasting blood glucose concentration [mean (SD)] before each test meal was similar when insulin lispro was administered pre- or postprandially [7.3 (2.6) mmol/l versus 6.3 (1.9) mmol/l,  $p=0.3$ ]. Between-subjects ANOVA showed that the order of the timing of the injection of insulin lispro had no effect on the resulting glycaemic excursions.

### *Preprandial administration of lispro*

Administration of insulin lispro before the high fat, solid-phase meal produced a cumulative decline in postprandial blood glucose, with a mean (SD) maximal decrement of 1.7 (2.4) mmol/l below baseline at 150 minutes (figure 9.1). When insulin lispro was administered before the test meal, hypoglycaemia developed in three subjects. In one subject, the premeal blood glucose was 5.9 mmol/l and fell progressively to 2.9 mmol/l at 150 minutes. In the second subject, the blood glucose fell from a premeal value of 6.8 to 2.7 mmol/l at 150 minutes. In the third subject, the premeal blood glucose was 5.1 mmol/l and fell progressively to 2.8 mmol/l at 240 minutes. Data from these subjects were included in the repeated measures analysis of variance over time as it is accepted practice to



**Figure 9.1** Mean  $\pm$  SE postprandial glycaemic excursions for high fat test meals. ■ postprandial administration of insulin lispro, ◆ preprandial administration of insulin lispro

employ a 'missing value' rule for the purpose of such an analysis [Burge, 1997b]. However, the mean plasma glucose concentrations for the post hoc analyses include values for only those subjects who remained in the study and do not include the derived data.

#### *Postprandial administration of lispro*

The glycaemic excursion over time was significantly greater when insulin lispro was administered after the test meal compared to before the meal ( $p=0.006$ ). Postprandial administration of insulin lispro permitted a rise in blood glucose after the meal with a mean (SD) maximal increment of 2.2 (1.3) mmol/l above baseline at 60 minutes (see figure 9.1). Hypoglycaemia did not occur in any subject when insulin lispro was administered postprandially. When insulin lispro was administered postprandially, the blood glucose excursions were significantly higher ( $p<0.01$ ) at the time points of 60 minutes and 150 minutes, compared with preprandial administration.

### **9.4 Discussion**

When the rise in blood glucose after a meal is delayed, the rapid onset of action of insulin lispro may promote the risk of early postprandial hypoglycaemia [Burge et al, 1997a]. The principal aims of the present study were to identify the optimal time of administration of insulin lispro before or after a high fat, solid-phase meal and assess the risk of developing postprandial hypoglycaemia over an extended period of 5 hours. It was surmised that the consumption of a high fat meal would delay the postprandial rise in blood glucose, and that greater synchronisation of the peak action of insulin with the postprandial rise in blood glucose would be achieved by administration of insulin lispro after the meal. Fried fish and french fried (chipped) potatoes was chosen as a test meal as it is high in saturated fat and is a popular dish in the UK.

The timing of the administration of insulin lispro in relation to the composition of a meal has been examined previously [Burge et al, 1997a, Strachan & Frier,



1998, Schernthaner et al, 1998]. Schernthaner et al [1998] used a test meal consisting of beef stroganoff and demonstrated that the postprandial injection of insulin lispro produced a glucodynamic pattern over two hours that was comparable to the effect of human soluble insulin given either 20 minutes before, or immediately before the meal. Burge et al [1997a] gave subjects a low-carbohydrate, high-fat breakfast coincident with the injection of insulin lispro and demonstrated that early postprandial hypoglycaemia occurred more frequently than when they were given soluble insulin 30 minutes before the meal. Strachan & Frier [1998] showed that when insulin lispro was administered after a high fat breakfast, either in solid or liquid form, postprandial blood glucose rose in most subjects and the risk of postprandial hypoglycaemia was minimal. The increments in postprandial blood glucose were relatively high, with a peak excursion of 3.6 mmol/l at 45 minutes when the meal was solid, and a peak excursion of 4.2 mmol/l at 45 minutes when the meal was liquid [Strachan & Frier, 1998]. However, the preprandial administration of insulin lispro before the high fat, solid-phase breakfast meal provoked a decline in blood glucose, so that by 120 minutes, mean blood glucose was 3.4 mmol/l below baseline concentrations, and three subjects developed overt hypoglycaemia.

In the present study, when insulin lispro was administered 20 minutes after a high fat meal, no evidence of a postprandial fall in blood glucose was obtained, congruent with previous observations [Strachan & Frier, 1998, Schernthaner et al, 1998]. However, the postprandial administration of insulin lispro did not compromise glycaemic control by producing postprandial hyperglycaemia; the mean rise of blood glucose was 2.2 mmol/l at 60 minutes after the start of the meal. This is probably related to the composition of the test meal which has a high fat component in solid phase, and contrasts with the relatively high liquid content of the test meal used in the study performed by Strachan & Frier [1998]. The postprandial injection of insulin lispro neither provoked unrestrained hyperglycaemia nor caused postprandial hypoglycaemia with this type of meal,



which is reassuring from a practical viewpoint. Thus, in the present study, administration of insulin lispro after the high fat meal resulted in a satisfactory glycaemic excursion over the subsequent five hours (figure 9.1) with no evidence of pronounced hyperglycaemia before the evening meal.

The preprandial administration of insulin lispro before this typical high fat meal provoked progressive hypoglycaemia in three subjects. The preprandial blood glucose concentration in these three subjects was between 5.1 and 6.8 mmol/l indicating good preprandial glycaemic control. In these individuals the presumed delay in gastric emptying associated with the high fat meal would result in a delayed rise in postprandial blood glucose and so exacerbate a mismatch between blood glucose concentration and insulin activity, thus promoting postprandial hypoglycaemia.

Gastric emptying is influenced by many factors other than the composition of a meal and, as noted earlier, the prevailing level of blood glucose influences the rate of gastric emptying [MacGregor et al, 1976, Fraser et al, 1990, Oster-Jorgensen et al, 1990, Schvarcz et al, 1993] and abnormalities of gastric emptying are common in people with diabetes of long duration [Keshavarzian et al, 1987, Wegener et al, 1990, Kong et al, 1996, Samsom et al, 1996, Lyrenas et al, 1997, Merio et al, 1997]. An attempt was made to control for these two factors by selecting subjects with relatively short duration of diabetes and with no symptoms of gastric stasis, and by ensuring that the blood glucose concentration before the commencement of study was within a narrow range (4-12 mmol/l).

In conclusion, when a meal contains a high content of fat in the solid-phase, administration of insulin lispro after the meal may reduce the risk of early postprandial hypoglycaemia, without compromising the postprandial control of blood glucose.

**Part V**  
**Concluding Comments**

**CHAPTER 10**  
**CONCLUSIONS AND FUTURE RESEARCH**

## **10.1 DETERMINING THE RELEVANCE AND VALIDITY OF COGNITIVE DYSFUNCTION IMPOSED BY ACUTE HYPOGLYCAEMIA**

The initial chapters of this thesis gave a comprehensive overview of the research that has accumulated over the last two decades on acute hypoglycaemia. It is clearly evident that acute hypoglycaemia causes an acute, reversible decline in mental capacity and that this can have a deleterious effect on the quality of life of people with diabetes [Deary, 1999]. However, previous studies have used cognitive tests and measures that were general in nature. Therefore, a major aim of this thesis was to try and determine the importance of these effects on a practical basis using a set of well-validated tests.

## **10.2 ACUTE HYPOGLYCAEMIA, ATTENTION AND INTELLIGENCE**

Studies 1 and 2 provided further insight into two areas that have previously been difficult to study. A validated test of attention that was designed specifically to measure multiple facets of attention, based largely on everyday materials and the use of real-life circumstances, was used to determine whether acute hypoglycaemia disrupts attentional functioning in both people with and without type 1 diabetes. There was a significant decline in tests of selective attention, both visual and auditory, and in attentional switching, in keeping with the received wisdom that psychological tests that involve rapid responses, and those which are more cognitively complex, are more likely to be affected by hypoglycaemia. However, contrary to previous work, it was shown that sustained attention to a repetitive, relatively boring stimulus was unaffected by a short duration of hypoglycaemia (ten minutes), although future efforts should look at tests of sustained vigilance. Crucially, it was shown that acute hypoglycaemia significantly impairs practical everyday activities such as reading a map, or determining which floor to stop in a lift.

An unexpected finding was the lack of a deleterious effect of acute hypoglycaemia on non-verbal reasoning. After considering the various possibilities that could have accounted for this result, the most likely conclusion

was that the Standard RPM were too easy for the chosen subjects, who comprised people whose mean was just above average intelligence, and thus a ceiling effect had been reached. This problem is occasionally encountered when using psychological tests during hypoglycaemia [Deary, 1993b]. As discussed in Chapter 7, this hypothesis has now been tested by Warren et al [2004] who repeated the study using the Ravens Advanced Progressive Matrices. Although they demonstrated a decline in non-verbal reasoning during hypoglycaemia with the more difficult test, the subjects in the study by Warren et al [2004] were of a higher premorbid intelligence (mean number correct score on NART was 40) compared with a mean number correct score of 27 in the study by McAulay et al [2006], thus introducing a possible confounder.

It would have been interesting to correlate symptoms of hypoglycaemia with cognitive performance but, given the low power (and likelihood of a type 2 statistical error) for this type of analysis, it was not performed. Similarly, a gender analysis would also have required a larger sample size. In keeping with this thesis, future research could examine the effects of acute hypoglycaemia on other basic brain processes. For example, this could be based on cognitive studies, such as memory and language function, psychophysics including sensory processing, or brain imaging, using positron emission tomography (PET), single photon emission tomography (SPET) or MRI. A study involving functional MRI has been published with a key finding that cortical activity was increased during a choice reaction task, raising the possibility of a compensatory mechanism to reduce higher cognitive dysfunction induced by hypoglycaemia [Rosenthal et al, 2001].

As discussed in Chapter 2, there are numerous proposed moderators of cognitive dysfunction during acute hypoglycaemia. The evidence derived from the present studies suggests that a diagnosis of diabetes may act as a susceptibility factor to cognitive disruption during hypoglycaemia. Further research to



understand the individual differences in the mental disruption caused by hypoglycaemia is welcome.

### **10.3 MOTIVATION AND SUBJECTIVE COGNITION DURING ACUTE HYPOGLYCAEMIA**

The perceived practice effect that may take place with tests of cognitive function during studies of hypoglycaemia has been a concern [Heller & Macdonald, 1996]. Furthermore, fatigue may increase the sensitivity of cognitive tests, in that those tests attempted at the end of a test period may be more sensitive to the effects of hypoglycaemia. Therefore, Study 3 is a useful addition to current understanding by demonstrating that motivation declined to a similar extent during both the euglycaemia and hypoglycaemia arms of the glucose clamp, thus supporting the results and conclusions of previous studies of hypoglycaemia. However, the main motivation dimension assessed by the DSSQ relates to intrinsic motivation, which reflects the extent to which the person is motivated by interest and engagement in task content. Therefore, further work could investigate additional dimensions, such as extrinsic motivation.

Research on the measurement of subjective states has been limited, focusing on one or two dimensions only, because cognition is a difficult aspect of state to assess due to the multiplicity of constructs that may be relevant, and Study 3 appears to be the first to examine subjective cognition in the setting of hypoglycaemia. Although the adverse effects of recurrent severe hypoglycaemia on cognitive function in people with diabetes has generated much debate [Deary & Frier, 1996], the issue of whether subjective aspects of cognition deteriorate has not been examined. While the present study was not intended to address this, given that there might be some slight long-term cognitive decrements on average among people with diabetes [Perros & Deary, 1999], it would be interesting to ascertain whether subjective aspects of cognition are also affected.

Although the cognitive tests in Study 3 were chosen because they engaged effortful cognitive processing (TEA) and had a relation to the person's general ability (RPM), little is known about the external validity of this study in terms of the real-life impact of hypoglycaemia on motivation and cognitive interference. Therefore, multimethod in-field assessment, such as experience sampling combined with continuous glucose monitoring would be worth further study. Future work could examine the associations between mood, symptoms, motivation and cognition, and the addition of data derived from counterregulatory hormone measurement, especially epinephrine data, would add interest. Moreover, it would be of value to correlate the symptoms of hypoglycaemia with many of the state measures, including the interference scales, but for reasons previously stated, our study sample of 16 subjects would not allow this.

#### **10.4 REDUCING THE FREQUENCY OF HYPOGLYCAEMIA WITH INSULIN ANALOGUES**

Although the flexibility in time of injection of insulin lispro may be of benefit during intercurrent illness and in situations where the quantity of food to be ingested may be unpredictable, because of the rapid onset of action of insulin lispro, the risk of early postprandial hypoglycaemia is increased in certain situations. This includes the ingestion of certain meal types, especially high fat, solid meals that are slowly absorbed. Study 4 demonstrated that the optimal time of administration of insulin lispro with a high fat meal (fried fish and chips) was after the meal in order to reduce the risk of hypoglycaemia, without compromising the postprandial control of blood glucose. This is of practical interest to those with type 1 diabetes who may be using insulin lispro and who eat such a meal, although current dietary recommendations would not encourage ingestion of this particular meal on a regular basis. Further study would be enhanced by controlling for antecedent glycaemia by use of an insulin infusion, thus ensuring that all subjects start with the same blood glucose value.

## 10.5 CONCLUSIONS

Hypoglycaemia will remain a major barrier to the management of insulin-treated diabetes for the likely future, as long as insulin delivery systems remain imperfect. Therefore, the measurement of cognitive function is relevant to diabetes management. In addition to those already mentioned, important areas for research include unraveling the mechanisms and finding treatments for impaired awareness of hypoglycaemia, and determining the moderators of cognitive change and its threshold during acute hypoglycaemia. The arrival of novel treatments such as islet cell replacement [Shapiro et al, 2000], human amylin analogues [Buse et al, 2002], GLP 1 analogues [Dupre et al, 1995] and immunotherapies [Bach 2001] will signal improvements for those who can access these treatments. However, for the majority of people with diabetes, the absence of a plasma glucose regulated insulin delivery system will mean that the problem of hypoglycaemia in diabetes will remain a difficult management issue for the future.

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## Appendix 1

### Abstracts and communications

1. Effects of acute insulin-induced hypoglycaemia on attention and intelligence in humans.  
**McAulay V**, Ferguson SC, Deary IJ, Frier BM.  
EASD meeting, Jerusalem, Israel, September 2000 (oral presentation).  
Abstract: *Diabetologia*, 2000; **43**: 6 (Suppl. 1)
2. The effects of acute insulin-induced hypoglycaemia on attention and intelligence in non-diabetic humans.  
**McAulay V**, Ferguson SC, Deary IJ, Frier BM.  
Scottish Society for Experimental Medicine, Glasgow, 2000.  
Abstract: *Scottish Medical Journal* 2001; **46**: 29-30
3. The effects of acute insulin-induced hypoglycaemia on attention and intelligence in subjects with type 1 diabetes.  
**McAulay V**, Sommerfield A, Deary IJ, Frier BM.  
Poster discussion, Diabetes UK, Glasgow, April 2001.  
Abstract: *Diabetic Med* 2001; **18**: 57 (Suppl. 2)
4. Optimal timing of administration of insulin Lispro in relation to ingestion of a high fat, solid phase meal in type 1 diabetes.  
**McAulay V**, Ferguson SC, Frier BM.  
Poster discussion, Diabetes UK, Glasgow, April 2001.  
Abstract: *Diabetic Med* 2001; **18**: 80 (Suppl. 2)
5. The effects of acute insulin-induced hypoglycaemia on attention and intelligence in people with type 1 diabetes.  
**McAulay V**, Deary IJ, Frier BM.  
EIFM, Edinburgh, UK, May 2001 (oral presentation).  
Abstract: *European Journal of Internal Medicine* 2001; **12**: 171 (Issue 3)

## Appendix 2

### Publications

1. Acute hypoglycemia in humans causes attentional dysfunction while nonverbal intelligence is preserved.  
**McAulay V**, Deary IJ, Ferguson SC, Frier BM.  
*Diabetes Care* 2001; **24**: 1745-1750
2. Attentional functioning is impaired during acute hypoglycaemia in people with type1 diabetes.  
**McAulay V**, Sommerfield AJ, Deary IJ, Frier BM.  
*Diabet Med* 2006; **23**: 26-31
3. Post-prandial administration of insulin Lispro with a high fat meal minimizes risk of hypoglycaemia in type 1 diabetes.  
**McAulay V**, Ferguson SC, Frier BM.  
*Diabet Med* 2004; **21**: 953-954
4. Effects of acute hypoglycaemia on motivation and cognitive interference in type 1 diabetes.  
**McAulay V**, Deary IJ, Sommerfield AJ, Matthews G, Frier BM.  
*J Clin Psychopharmacol* 2006; **26**: 143-51